ANGLIA RUSKIN UNIVERSITY

A NOVEL INTERMITTENT PNEUMATIC COMPRESSION BOOT TO IMPROVE VENOUS HAEMODYNAMICS

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Abstract

Venous ulcers, caused by venous hypertension, affects 0.5-1% of the general population (up to 640,000 Britons), especially the elderly with poor mobility. This common malady is difficult to manage, expensive to treat, and often recurs. Common treatments include external static (bandage) and dynamic (Intermittent Pneumatic Compression (IPC)) compression. Although several important applications for IPC have emerged, the optimal magnitudes of cuff pressures and related timing parameters have not been determined.

The primary goal of this dissertation was to investigate the sensitivity of the healthy cohort's haemodynamics to changes in cuff pressure magnitudes and timing parameters. This study measures the velocity-time integral to assess venous flow changes. i) the optimum pressure to maximise venous return, ii) the optimum deflation time that will maximise venous return and iii) whether IPC should be personalised to patients.

More analytically this thesis explores:

1. the relationship between cuffs' pressure and velocity time integral (stroke distance) during IPC
2. the haemodynamic effects of IPC across genders and ages
3. the impact of deflation time across different set of cuff pressures, gender and ages.

A novel IPC device was designed and prototyped to provide adjustable parameters (pressures, time), safety, and reliability. This device used a real-time, non-invasive method (Doppler ultrasound) to collect data on the haemodynamics of the popliteal vein. After several preliminary tests to help define IPC design and device reliability, forty healthy participants were recruited and tested, using different sets of compression pressures and cuff inflation and deflation timing values.

Strong positive relationships between cuff pressure magnitude and mean stroke distance was observed for deflation times of 10 seconds (Stroke distance of 234, 434 and 557 AU for pressure magnitudes of 60, 80 and 100 mmHg, an increase of 86% from 60 mmHg to 80 mmHg and 28% from 80 mmHg to 100 mmHg; $p<0.001$, $R=0.620$), 20 second (Stroke distance of 263, 430 and 596 AU for pressure magnitudes of 60, 80 and 100 mmHg, an increase of 96% from 60 mmHg to 80 mmHg and 21% from 80 mmHg to 100 mmHg; $p<0.001$, $R=0.629$), and 30 second (Stroke distance of 274, 451 and 628 AU for pressure magnitudes of 60, 80 and 100 mmHg, an increase of 108% from 60 mmHg to 80 mmHg and 17% from 80 mmHg to 100 mmHg; $p<0.001$, $R=0.609$).

Mean stroke distance did not saturate at 80mm Hg and was not significantly related to deflation times, irrespective of the magnitude of applied cuff pressure, but did saturate below 20-second deflation times. Mean stroke distance was not affected by gender or age across deflation times and pressure levels.

To conclude, the main determinant of haemodynamic effects was the magnitude of cuff compression pressure, irrespective of sex or age. The optimum compression pressures in the standing position to obtain maximum stroke distance were the set of 120/100/80 mmHg for the ankle/lower calf/upper calf levels respectively. The value of foot compression was negligible. This investigation sets the foundation for future research in pathological groups and further refinement of this technology.

Keywords: Venous Ulcers, Deep Venous Thrombosis, Venous Hypertension, Intermittent Pneumatic Compression, Doppler Ultrasonography

Contents

Chapter 1 - Introduction

1.1 Venous Insufficiency

The adoption of erect position as an evolutionary achievement seems to have challenged human physiology and biomechanics. Humans are the only mammals suffering from venous ulcers. The classic example of the giraffe which, despite the long column of blood from its distal leg to the level of its heart, never develops venous ulcers is a powerful demonstration of evolutionary achievement: giraffe’s legs are protected by very hard, tight skin that would not allow development of significant soft tissue oedema. Under this inflexible skin that acts as a natural compression system, all muscle activity, and movement become highly efficient in terms of muscle pump-triggered venous return. (Pedley 1987 and Hargens 1987).

Porter (1988) and the Subcommittee on Reporting Standards in Venous Disease defined Chronic Venous Insufficiency (CVI) as an abnormally functioning venous system caused by venous valvular incompetence with or without associated venous outflow obstruction which may affect the superficial system, the deep system or both and may result from congenital or acquired processes. The same group explains that the most common clinical presentation of superficial chronic venous insufficiency is varicose veins and on the CEAP classification system (developed and introduced in 1994 by an international consensus conference) is classified as CEAP Class 2.

Nicolaides (2000) in a consensus statement on the investigation of chronic venous insufficiency describes the symptoms of heaviness, aching, cramps itching, burning, swelling, dilatation of superficial veins and skin changes that are associated with chronic venous insufficiency. He explains that CVI symptoms are a produced by venous hypertension as a result of structural or functional abnormalities of veins.

From this point of view the long-term dermal complications of chronic venous insufficiency, namely lipodermatosclerosis – from the Greek “fat” (lipo) and “skin” (derma) “hardening” (sclerosis) – can be seen as the body’s defense against the detrimental effects of venous hypertension. Indeed, the skin around the lower calf slowly hardens circumferentially around the area of high venous pressure. Unfortunately, the skin transformation is eventually complicated with localized skin breakdowns – small initially but with a tendency to expand - that in due course progress into larger areas of exposed subcutaneous tissues forming ulcers. External compression of the leg is an attempt to fill this gap in evolution and physiological defense response. The rationale for compression extends beyond this point.

1.2 External Factors Contributing to Venous Insufficiency

Behavioral, social and technological changes have resulted in an inactive lifestyle which, in combination with the great increase in life expectancy and the worldwide expansion of in-hospital healthcare, created an epidemic of deep venous thrombosis. Humans of any age unable or unwilling to walk, after a surgical operation or prolonged immobilization, elderly and ill are prone to development of thrombi in the leg veins. Thrombi can be life threatening if they detach, travel through the circulation system and block significant parts of the lung vessels. People with a tendency to develop these thrombi are treated preventively either with the administration of anticoagulant agents (Gordon 2012) or external leg compression (Dennis 2013), or, often, both (Kakkos 2008).

1.3 Compression: A Treatment for Venous Insufficiency

External compression also has applications for managing lymphoedema which is caused an accumulation of fluid in the arms or legs following infections or, more commonly, after operations for cancer. Leg compression may be employed for several applications; each one is based on different physiological mechanisms and different philosophies of treatment. All compression-based treatments, however, ultimately aim to achieve the same objective: to keep the blood moving. Blood stagnation in leg veins can cause thrombosis and can increase venous blood pressure with detrimental consequences ranging from mild symptoms to extensive leg ulcerations. External leg compression creates a relatively tight sheath in which the calf's musculo-venous pump's function is enhanced and the venous blood moves faster.

Broadly speaking, in the case of venous return, as Hippocrates stated, "motion is life".

The approaches to external leg compression include static and dynamic methods. Static compression is an attempt to improve the human leg's skin function by supporting it with an external layer of tight material (mimicking the giraffe’s skin (Hargens and Pedley (1987)).

Dynamic compression aims to enhance (in some cases replacing) the physiological mechanisms of venous blood return through the actions of the calf muscle pump (Simka 2004) and venous foot pump (Gorley 2010).

The principles of compression for the treatment of venous ulcers were known very early in the history of medicine. Hippocrates, who himself suffered from leg ulcers, wrote, “in the case of an ulcer is not expedient to stand, especially if the ulcer be situated on the leg" emphasizing the importance of reducing the amount of blood pooling in the leg veins.

1.4 The Evolution of Intermittent Pneumatic Compression Devices

Over the following centuries, the use of dressings that protected and, at the same time, compressed and hid the ulcerated legs became more common practice. It was only in the second half of the twentieth century, however, when a new way of applying leg compression appeared. Collens and Wilensky described in 1936, ahead of their time, the use of an intermittent venous pneumatic compression device for the treatment of, not venous, but peripheral arterial disease, using the phenomenon of reactive hyperemia. Peripheral vascular disease was later to become one of the main contraindications to intermittent pneumatic compression for the treatment of venous ulcers. Although during the same time, research and advances in the field of arterial diseases were ground-breaking, old dogmas continued to define the practice around venous diseases and particularly leg ulcers.

The rise of the pneumatic splints for fractures of the lower and upper limbs, in the sixties, revived the interest and the research into external pneumatic compression for venous insufficiency, lymphoedema, and prevention of deep venous thrombosis. In 1970, Calnan published their work titled “Intermittent pneumatic compression legging simulating calf-muscle pump” in The Lancet, signifying the start of more rigorous research on the topic and drawing industry attention to the current sector today known as Intermittent Pneumatic Compression (IPC) devices.

Although IPCs have evolved, their progress was not as dramatic as that of technological advances in medicine. What has, however, accelerated the recent evolution of this technology has been the necessity for effective management of venous ulcers and the life-threatening phenomenon of deep venous thrombosis. A whole new generation of IPC devices have emerged to respond to this need and the related research is to source for the majority of existing IPC literature.

1.5 Structure of the Thesis

This chapter sets the stage by describing the demographic, anatomical, physiological and pathophysiological background behind conditions that eventually lead to chronic venous insufficiency, venous hypertension, oedema, lower leg skin changes and, subsequently, ulceration. Further information is provided with regards to diagnostic modalities including old, new and experimental treatments.

The modern applications of IPC are far from limited in the treatment of venous ulcers. Widely regarded as an adjunct method for deep venous thrombosis prophylaxis, IPC devices are used routinely in intensive care units, during surgical procedures and postoperatively in recovery settings. Further indications include lymphoedema, arterial disease, and sports recovery.

This is an in-depth study of the haemodynamic consequences of a unique IPC device with a fully-adjustable function, specifically designed for the needs of this thesis and aspires to explore uncharted territories of IPC technology. The study is divided into the following three phases:

1. The preliminary phase, which consists of the literature review and a survey of current practices of IPC devices.
2. The middle phase, which consists of the rationale and methods used to design, create and test a novel IPC device
3. The final phase which consists of the analysis of results from testing and discussion of those findings.

These are outlined and described below.

The basic principles of anatomy and physiology of the lower limb venous system and the contemporary knowledge and status of IPC technology with particular emphasis on its haemodynamic effects are discussed in chapter 2. The overarching aim of this research is to improve the function of IPC technology towards the goal of achieving more effective compression in terms of enhancement of the lower limb venous haemodynamics.

1.6 Gap in Knowledge

Although the beneficial clinical effects of IPC have been documented and there is already a place for this technology in everyday clinical practice, the optimal parameters used for maximizing effects remain the subject of current research. One challenge is the difficulty associated with assessing changes in the venous blood flow non-invasively, but effectively. Widely accepted methods of measuring the flow alterations during IPC are duplex ultrasound, plethysmography, and phlebography. Each one of these approaches have their advantages and disadvantages. Phlebography is invasive and requires vein catheterisation. Duplex ultrasonography requires accurate positioning and adherence to the point of scanning. This is difficult to achieve for a long period of time as the necessary conductive gel causes the ultrasound probe to slide away from the point of scanning.

To fill the gap in knowledge around the haemodynamic effects of IPC technology is addressed in this thesis by introducing a novel highly-adjustable IPC device with a new method of assessing the changes in popliteal vein blood flow during IPC action. This method utilises the already established in the field of echocardiography parameter of Stroke Distance. Stroke Distance is the Velocity-Time Integral (VTI) of a haemodynamic event, recorded by a Doppler scanner (detailed in section 2.5). The Doppler probe used in testing was a miniature flat probe secured in a way to remain in the same exact position during the length of time of testing with different pressure and times settings.

1.7 Hypotheses

The following hypotheses were formulated:

H1A Mean stroke distance will increase with IPC cuff pressures for each cycle. Accept H1A if $p<0.05$ for the linear regression, $R>0.5$. A linear positive relationship ($p<0.05$) exists between mean SD and IPC pressures with an $R>0.5$

H1B Mean stroke distance will saturate for compression pressures beyond 80mmHg. Accept H1B if the SD is <5% different at 100mm/Hg compared with 80mm/Hg

H1C The mean stroke distance across IPC pressures will not be significantly different between male and female participants. Accept H1C if there's no difference via ANCOVA in mean stroke distance between males and females accounting for weight and height

H1D The mean stroke distance across IPC pressures will not be affected by the participants' age. Accept H1D if there's no difference via ANCOVA between those above the median age and those below the median age accounting for differences in weight and height

H2A The mean stroke distance will increase with increasing deflation time intervals between subsequent IPC compression cycles. A linear positive relationship ($p<0.05$) exists between mean stroke distance and deflation time interval with an $R>0.5$. Note*: there's a maximum deflation time interval = 30 sec

H2B Mean stroke distance will saturate below 20 second deflation time intervals between IPC subsequent cycles

H2C Mean stroke distance across deflation time intervals will not be significantly different between male and female participants

H2D The mean stroke distance across deflation time intervals between subsequent IPC cycles will not be affected by the participants' age

Chapter 2 - Literature Review

2.1 The lower limb venous circulation

The venous part of the human circulatory system carries 90% of the blood of the lower limbs and is responsible for the return of the blood from the peripheral tissues back to the right chambers of the heart (Ellis, 1990). From there, it is propelled to the lungs where it is enriched with oxygen, then to the left chambers of the heart and, from there, to the organs and tissues through the arterial system.

2.2 Anatomy of the lower limb veins

Veins, like arteries, consist of three layers - adventitia, media, and intima. The venous wall, however, is much thinner than the arterial wall (Figure 2.1). Their thin, elastic (compliant) wall allows them to, both, collapse and expand to a certain point to accommodate a large volume of blood.

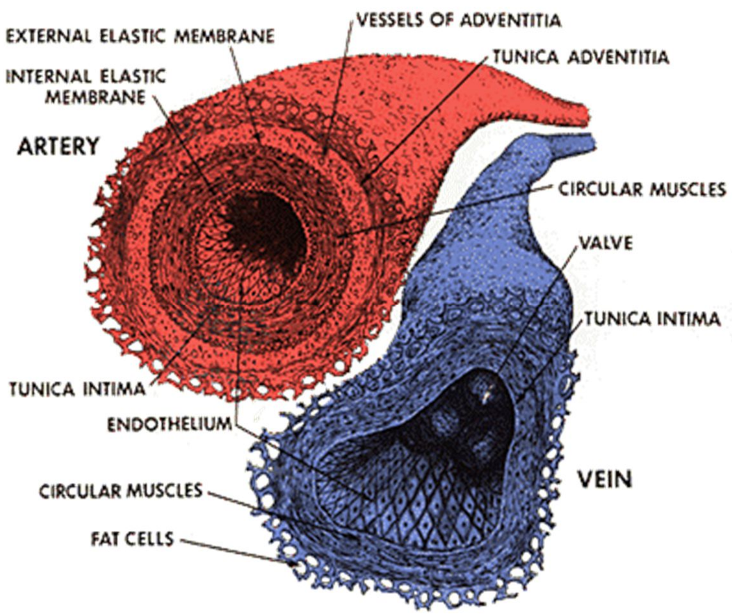


Figure 2.1: Anatomy of the vein compared to the artery, demonstrating the differences in wall thickness, compressibility and the presence of valves in the vein (Source: www – not copyrighted)

During prolonged periods of rest or immobility, the amount of blood pooling in the lower limbs veins increases and stagnation can lead to the formation of thrombi resulting to Deep Venous Thrombosis (DVT).

2.2.1 The superficial venous system

The lower limb veins form two anatomically distinct systems: a deep and a superficial one. The latter consists of veins located under the skin gradually connecting together to create two main trunks: the lesser (or short) and the greater (or long) saphenae veins.

The two saphenae veins join the deep veins at the level of the knee (short saphenous drains into the popliteal vein) and the groin (long saphenous drains into the common femoral vein). The anatomical entities at the points of connection are known as the saphenopopliteal and saphenofemoral junctions respectively.

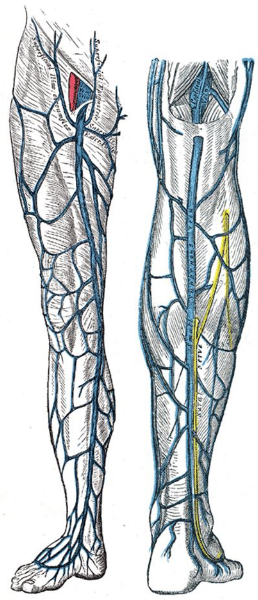


Figure 2.2: The superficial venous system of the lower limb. The greater (or long) saphenous and the lesser (or short) saphenae veins are the main superficial trunks and they join the deep system at the level of the groin and knee respectively. (Source: Gray’s Anatomy, out of copyright)

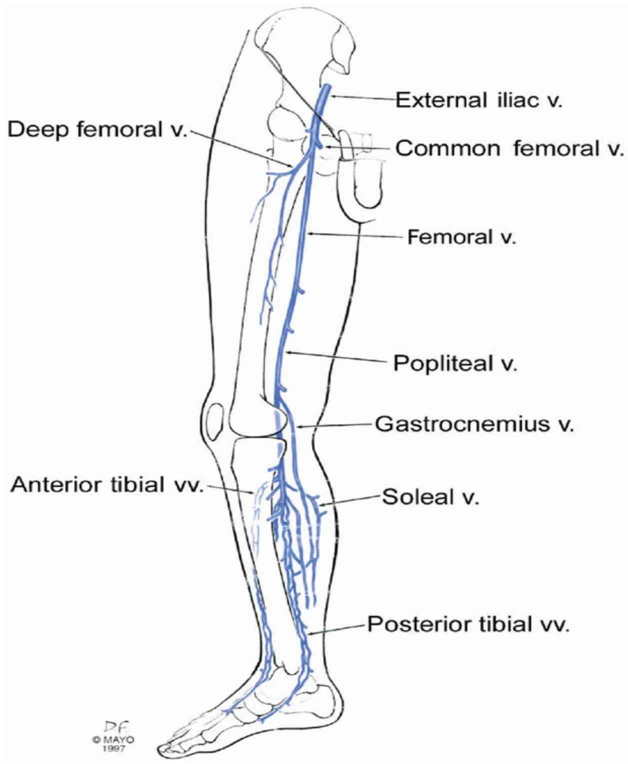


Figure 2.3: Deep venous system of the lower limb. The popliteal vein is illustrated as the main venous stem draining the lower limb at the level of the knee (Source: Mayo Clinic Image Library, 1997, with permission)

2.2.2 The deep venous system and network

Starting from the foot and following the blood flow proximally (to the heart), there are four major anatomically distinct but structurally continuous deep venous networks that carry the main volume of blood: the soleus and gastrocnemius venous network, the popliteal vein, the femoral and deep femoral veins and the perforating veins.

i. The soleus and gastrocnemius venous network

The large muscles of the calf contain a network of medium size veins that form an important anatomical and physiological entity, the Gastrocnemius Venous Network (GVN). These veins that are located in and between the muscles, host a significant amount of blood which is propelled cephalad (upwards) when the muscles contract (eg during walking or tiptoe maneuvering). This functional unit is commonly known as the “calf muscle pump” and plays a very important role in the return of the venous blood from the peripheries to the heart.

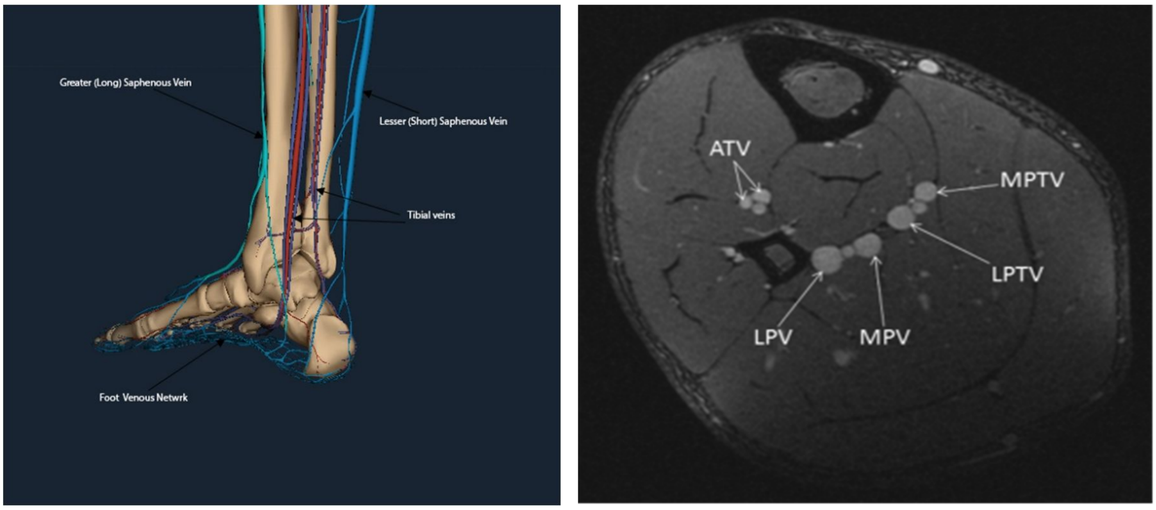


Figure 2.4: Deep veins of the calf: 3D and MRI image cross section. ATV: anterior tibial vein; LPV/MPV: Lateral/medial peroneal veins; LPTV/MPTV: Lateral/medial posterior tibial veins

(Source: Left: Anatomy Software reconstruction generated by the author, Right: Elsevier copyright, permission requested)

Aragao (2006) demonstrated that the majority of the main gastrocnemius venous trunks drain directly into the popliteal vein, making it the main venous trunk at the level of the knee. Kageyama (2008) showed that the soleal vein contains over ten multibranched veins in each leg. These veins are subclassified into three groups: (1) centralis, (2) medialis, and (3) lateralis. Each pair of the calf veins eventually connects together to form larger venous trunks forming eventually the popliteal vein trunk (Fig 2.5).

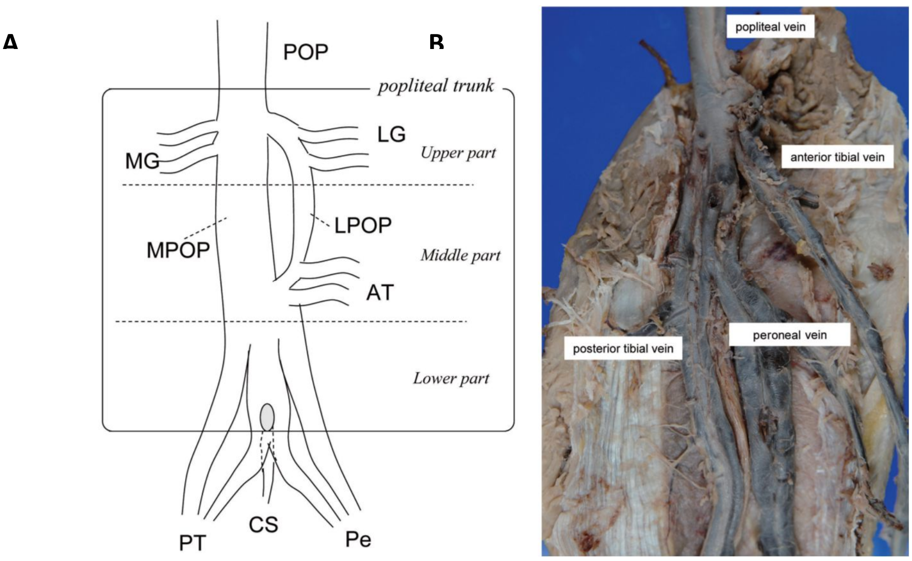


Figure 2.5: Schematic Drawing (left) and cadaveric dissection (right) of the popliteal trunk and the deep veins of the calf. The depiction of the way the deep

calf veins merge to create the popliteal vein (POP) which is the main stem of venous return at the level of the knee joint. All deep veins are surrounded closely by muscles – the physiological unit of calf musculovenous pump (Annals of Vascular Disease, Copyright Medical Tribune Inc, permission requested)

ii. The popliteal vein

The vast majority of the amount of the venous blood of the calf (85%) is drained through the popliteal vein at the level of the knee. This vein is formed by the joining of posterior and anterior tibial and peroneal and soleal veins, the main deep veins in the calf. A relatively large, superficial vein, the small (or short) saphenous vein joins the popliteal vein just above the junction of the popliteal and tibial veins at the level of the knee joint (Figure 2.6).

The most interesting characteristic of the popliteal vein from the scope of this thesis is its anatomical position in the popliteal fossa (the area behind the knee joint). At that level, the popliteal vein is located very superficially (1-3 cm beneath the skin, depending on the body habitus), allowing relatively easy access for a Doppler sensor. In addition, its position, immediately laterally to the popliteal artery, makes it easy to detect it as soon as the arterial signal is traced. These characteristics make it possible to detect blood flow in in the popliteal vein.

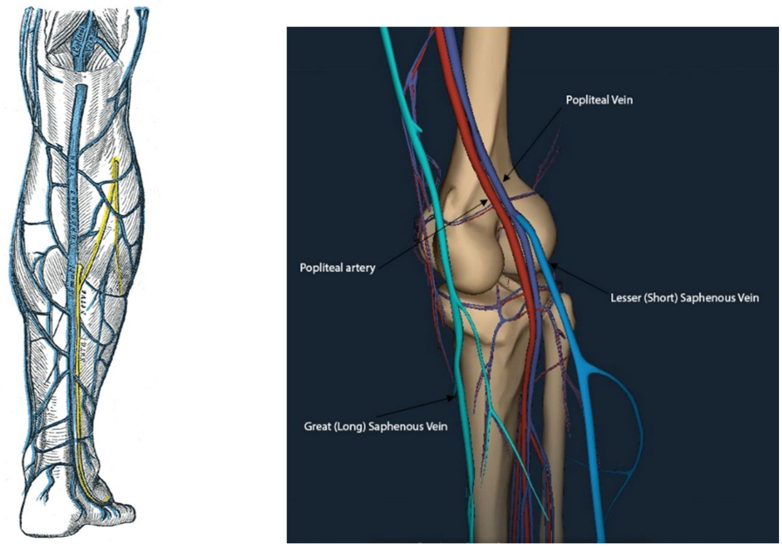


Figure 2.6: Popliteal vein: position in the popliteal fossa and relation to surrounding structures (Source: Left: Gary's Anatomy- out of copyright, Right: Anatomy Software reconstruction generated by the author)

iii. The femoral and deep femoral veins

The popliteal vein continues higher in the thigh as the femoral vein and its course lies next to that of the superficial femoral artery in the adductor canal (an anatomic tunnel between the large thigh muscles) to the level of the groin. Another large vein, the deep femoral vein, drains the venous blood of the major thigh muscles into the femoral vein at the level of the inguinal ligament. A number of researchers studying the haemodynamic effects of compression chose the femoral vein at the level of the groin as the point of imaging to check flow changes. The femoral vein at that level is easily accessible as it lies superficially and located anteriorly (in the front of the body).

iv. The perforating veins

The two venous systems (deep and superficial) communicate at several other levels both at the area of the calf and the thigh (Figure 2.7). The short veins connecting the two systems are known as perforating veins or perforators as they "perforate" the fasciae (hard fibrous membranes) that lie between the two systems (Meissner, 2005)

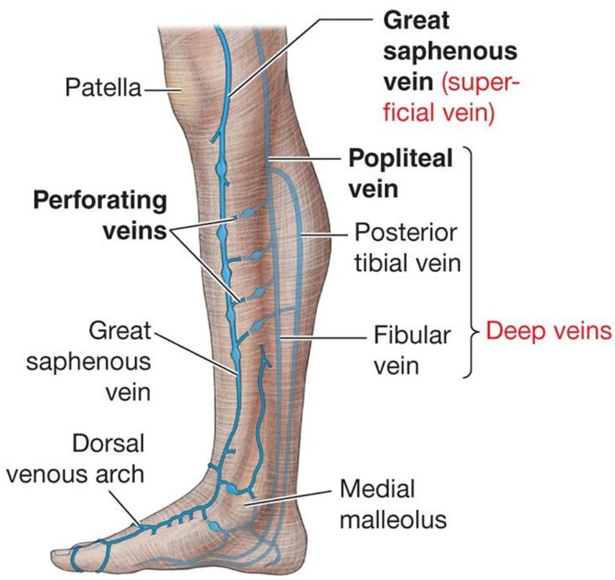


Figure 2.7: Perforating veins in the calf; (Lippincott and Williams, permission requested)

2.3 Physiology of lower limb venous circulation

Human tissue oxygenation is dependent on smooth and uninterrupted blood circulation. Oxygen-rich blood is returned via the pulmonary veins from the lungs to the left heart chambers. Subsequently, blood is propelled via the aorta and its branches to the peripheral tissues where the oxygen is consumed at the level of the capillaries.

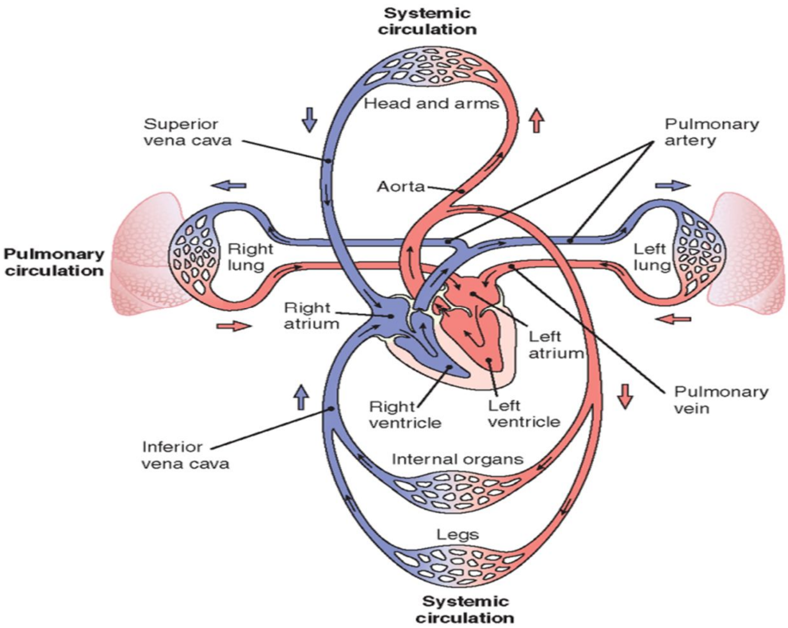


Figure 2.8: Arteries, capillaries, veins, heart, and lungs: the human circulation; Adapted

The small post-capillary vessels form the venules, the smallest size veins which, joining together, form medium and, subsequently, large size veins. Guyton (2015) describes veins as conduits for transportation of blood back to the heart. Their other important function is to serve as a controllable reservoir of additional blood that can be used in periods of demand. The same author estimates the volume of blood flowing at any point in the venous system to be approximately 54% of the total body's blood volume.

The low oxygen venous blood returns to the heart's right chambers via the complex venous network described in the anatomy section. In the case of arteries, the force that keeps the blood moving is mainly a result of the function of the left ventricular contractions. The driving force behind the blood flow in the veins is the sum of a number of physiologic mechanisms with different degrees of contribution (see below).

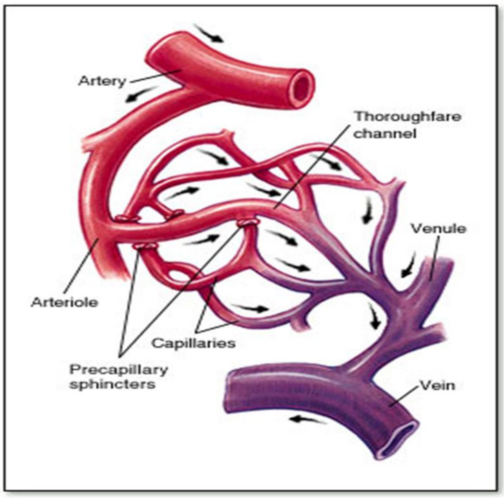


Figure 2.9: Arteries, arterioles capillaries, venules and veins

2.3.1 Fluid dynamics of the human venous circulation

i. Blood flow velocities and cross-sectional areas

Guyton 2015, comparing the cross-sectional areas of arteries and veins (Table 2), highlights the fact that the vein area averages four times that of corresponding arteries, which explains the large blood storage capacity of the venous system.

Table 2. Vessel cross sectional area; (Guyton and Hall, Physiology, Elsevier, permission requested)

Vessel Cross-Sectional Area (cm2)
Aorta 2.5
Small arteries 20
Arterioles 40
Capillaries 2500
Venules 250
Small veins 80
Vena cava 8

As the same volume of blood (F) passes through each part of the circulation per unit time, blood flow velocity (V) is inversely proportional to cross-sectional area (A):

$V = F/A$

Although aortic blood flow velocity averages 33 cm/s (resting conditions), blood flow velocity in the small veins (e.g. popliteal vein) is only 1/32 as rapid (about 1 cm/s).

ii. Flow through collapsible tubes

Venous flow is achieved through the interaction of the veins with their surrounding structures and a number of physiological mechanisms mainly consisting of muscle pumps. Katz (1969) explains that effective venous return cannot be achieved without the presence of a central pump (heart), a pressure gradient, a peripheral venous pump (muscle calf pump) and intact venous valves. The physiological effects of gravity and hydrostatic pressure oppose return venous flow in the upright position. Alimi (1994) argues that presence of competent valves, an efficient distal (calf/foot) pump mechanism, and an existing pressure gradient overcome gravity successfully.

The human circulation consists of a closed system of arteries, veins, and the heart. The circulating blood moves primarily because of the dynamic pressure gradient generated by the pumping action of the heart. Secondarily there are additional contributions from of the respiratory and muscle pumps that promote blood movement in the veins. In a normal human circulatory system, the hydrostatic pressure at the venous end of the capillaries ranges between 12 to 18 mmHg and gradually falls to 4-7 mmHg close to the right atrium. In the supine position, where gravitational forces are minimized, blood flows between these two pressure gradients.

Meissner (2007) explains that the weight of the blood column below the right atrium defines the hydrostatic pressure in the veins of the extremities. Gravitational and hydrostatic pressures are represented as a constant index (0.77 mmHg/cm) multiplied by the vertical distance in cm below the right atrium (Figure 2.10). On a still, sitting or standing subject the intravenous pressures of the lower limbs are higher. Alimi (1994) describes that, during inspiration, diaphragmatic contraction increases intra-abdominal and lower extremity venous pressure. Ascites (presence of fluid in the abdomen) and obesity produce similar increases in pressure, even when supine.

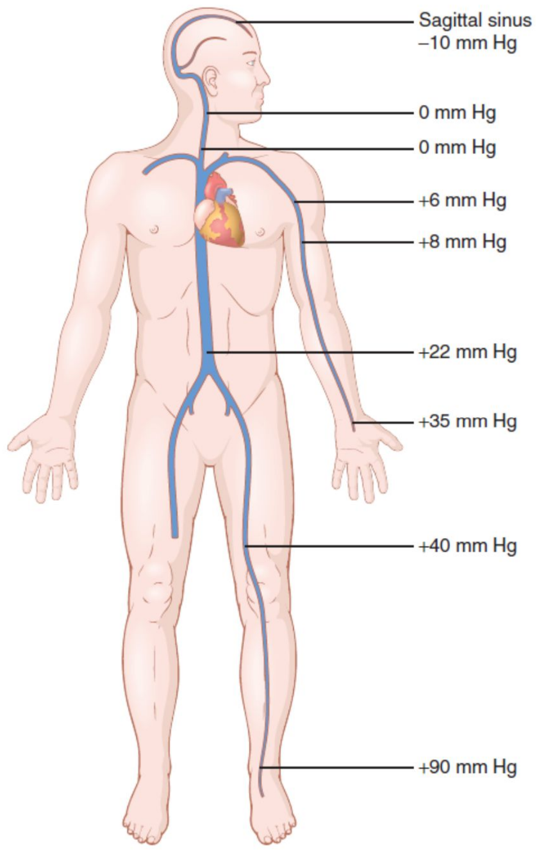


Figure 2.10: Effect of gravity on the venous pressures at different body levels for a standing adult of average height (Guyton and Hall, Textbook of Medical Physiology, 2015, permission requested)

Venous blood circulation in the dependent lower limb takes place with the ejection of blood with the help of the muscle pumps and the prevention of reflux by competent valves. The valves, in addition, divide the hydrostatic pressure by functionally dividing segments of the vein. The greatest number of valves is observed in the infra-popliteal veins, suggesting their functional importance. Interestingly, foot perforating veins, where the bi-directional flow is considered normal, do not have valves.

Chien (2008) describes that wall shear stress (WSS) is a factor that regulates blood vessel structure and influences the development of vascular pathology. DVT occurs in areas where blood flow is slow and changes direction, such as venous valve pocket. Very low WSS triggers the formation of microthrombi on the venous endothelium, but consistent blood flow; moderate levels of WSS have been shown to be important in maintaining a smoothly functioning vascular system.

2.3.2 The cardiac and respiratory pumps

There is a low-pressure gradient in the right atrium compared to the pressure in the vena cava. This causes shifting of the venous blood to the right atrium and, subsequently, to the right ventricle. Inspiration creates a negative pressure gradient in the chest and the abdominal cavity, causing flow of venous blood towards the heart. In addition, the right atrium pressures are very dependent on the levels of intrapleural (the space between the thoracic organs and the chest wall) pressures.

During inspiration, as the diaphragm descends and the chest wall expands, the pressure in this space drops. This phenomenon causes the lungs, the large veins in the chest, and the chambers of the right heart to expand. This expansion creates a low-pressure gradient in the thoracic superior and inferior vena cava and the right atrium, thus enhancing the venous blood return. An increase of the rate and depth of respiration increases the return of the venous blood to the heart.

2.3.3 The venous system pump - Venous compliance

Blood vessels have the ability to contract and expand, responding to changes in intraluminal pressures. The ability of an artery or vein to increase its diameter, and hence its volume, as a response to a change to the transmural (internal minus external) pressure is quantified as vessel compliance. Compliance (or capacitance) describes the distensibility of blood vessels. It is inversely related to elastance (or stiffness). The greater the proportion of elastic tissue in the wall of the vessel, the elastance becomes higher and the compliance becomes lower. A mathematical depiction of this is illustrated as:

$$C = dV/dP,$$

where C is compliance, dV is the change in volume and dP is the change in pressure. This equation describes how volume changes in response to a change in pressure. Neglen (1995) showed that the pressure/volume relationship of the calf veins is linear and shifts of the pressure/volume curve are likely to be predominantly caused by vein wall changes. Compliance is significantly greater for veins than for arteries. Consequently, more blood volume is contained in the veins than in the arteries. It is estimated that, at any point, 70% of the blood volume is contained in the venous system.

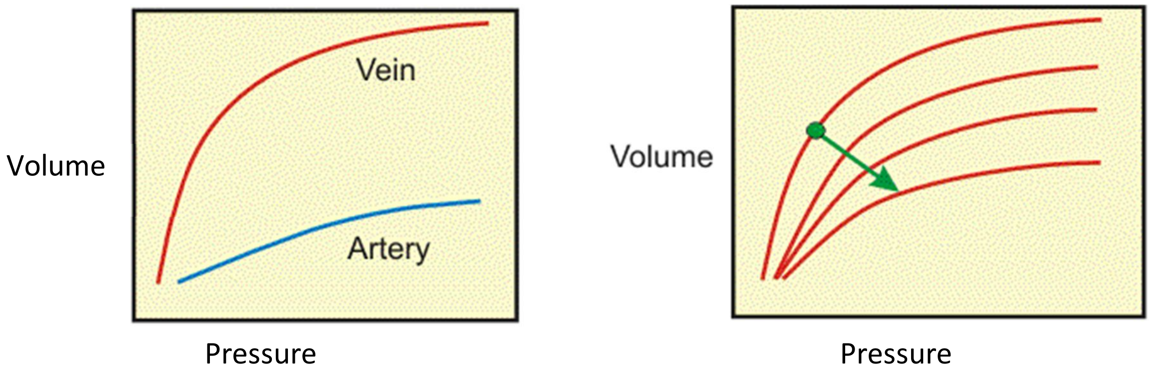


Figure 2.11: Veins have a much higher (up to thirty times) compliance than arteries of the same size and hence can expand to host a significant amount of blood

2.3.4 The calf muscle venous pump

The calf muscle pump is the most important mechanism contributing to lower limb venous return and has been the object of vigorous research and of many attempts to mimic its function – including the present work. Abadi (2007) showed that under- or no utilisation of the calf muscles results in higher chances of developing lower leg skin changes and ulcers.

Fegan (1964), was among the first researchers to acknowledge the clinical importance of the calf pump failure followed in the eighties by others, including Browse in 1988. The concept of the calf muscles surrounding deep veins and enhancing blood flow by contracting has been compared with that of the function of the heart as a pump. Christopoulos (1989) studied further the function of the calf muscle pump in relation to venous ulceration and showed that reproducible measurements of its efficacy are possible. Alimi (1994) looked into the relation of the calf muscle and deep vein pressures, using an invasive protocol and showed that there is a direct correlation between them.

Nicolaides (2000) highlights the importance of calf muscle pump in a consensus document, stating that anatomic prerequisites for the calf pump system to function properly are often neglected in the clinical evaluation of Chronic Venous Insufficiency (CVI). The same researcher states that a deficient calf pump is likely the key factor for the high rate of CVI among elderly persons.

Tierney (1993) studied the effect of ankle fractures to venous dysfunction by measuring functional venous volume, Venous Filling Index (VFI), Ejection Volume Fraction (EVF) and Residual Volume Fraction (RVF), using air plethysmography, and found strong positive correlation with significant and prolonged impairment in venous pump function following ankle fracture. A normal plantar arch, normal ankle mobility and normal painless calf muscle action are required for normal venous calf pump function (Nicolaides, 2000). Browse (1988) highlights that clinical evaluation of CVI should include assessment of the ankle joint and check for the presence of any associated muscular, articular, or neurological disease.

The stasis of blood in the lower limb veins in the upright position is limited by the compliance of the venous wall, the function of the venous valves and the action of the calf muscle pump. Meissner (2005) explains that approximately 90% of the lower limb venous return is achieved through the deep veins with the action of the foot, calf, and thigh muscle pumps. The fasciae (tough, non-flexible tissue sheets encasing the muscles) constrain the muscle groups during contraction and allow high pressures to be generated within the muscular compartments.

Meissner (2005) points out that the ejection fraction of the calf muscle pump is 65%, whereas that of thigh only 15%. During contraction of the calf muscles, the pressure in the posterior compartment can rise up to 250 mmHg, the veins are emptied of blood and resting venous pressure drops. The pressure in the posterior tibial vein (one of the largest veins in the calf) decreases from 80-100 to less than 30 mm Hg. A reduction in deep venous pressure during the post-contraction relaxation phase triggers flow from the superficial to the deep system through the perforating veins. Reflux or pathologic retrograde flow occurs when the valves are absent or incompetent. Meissner (2005) explains that in this case, retrograde flow during calf muscle relaxation prevents a reduction in pressure and the deep veins fill fast due to retrograde flow of blood in addition to the normal slow capillary inflow.

The severity of chronic venous disease is closely related to the magnitude of venous hypertension, as measured through a 21-gauge dorsal foot vein needle after 10 tiptoe manoeuvres. Nicolaides (1993) demonstrated that ulceration usually does not occur at ambulatory venous pressures less than 30 mm Hg, but the incidence is 100% at pressures greater than 90mmHg. However, the determinants of ambulatory venous pressure are complex and include venous reflux as well as obstruction and calf muscle pump dysfunction.

Back (1995) adds that ineffective calf muscle pump function is associated with a higher incidence of ulceration and increased non-invasive indices of venous pressure. Araki 1994 explains that, although the relationship with disease severity has not been consistent, the calf muscle pump ejection fraction is lowest in limbs with active ulceration (35%), followed by limbs with healed ulcers (49%) and those without ulceration but with duplex evidence of reflux (53%).

Meissner (2005) argues that this observation may be related to the progressive decrease in ankle range of motion with increasing severity of the disease. Back (1995) showed that lower limbs with chronic venous insufficiency have a limited range of motions in the ankle joint and this range decreases with the increasing severity of the clinical symptoms. They concluded that the limited range of movements is associated and possibly contributes to poor muscle pump function.

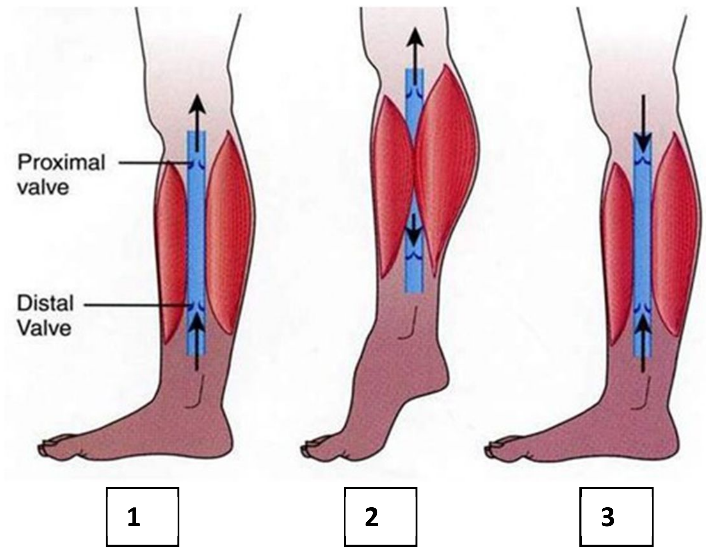


Figure 2.12: The calf muscle pump 1**.**The onset of muscle contraction 2. Muscle contraction and deep vein compression with proximal valves open and blood propulsion cephalad while peripheral valves close. 3. Closed valves prevent reflux. *Non-copyrighted image*

The calf muscle pump functions when the muscles contract and blood in the deep calf veins is propelled to the heart. The venous valves prevent reflux (retrograde flow) when the muscles are in relaxation phase. Muscle contraction produces a driving pressure of 90 mmHg.

2.3.5 The foot venous pump

The second most important (after the calf muscle pump) mechanism of venous return and the first in terms of timing sequence is the venous pump of the foot. The clarification of its role it was considered particularly important because if the foot venous pump contributed dramatically to the leg's venous return, then simple function, small size, foot-only IPC devices could be used effectively to solve the problem.

There have been a number of anatomical research studies that demonstrated the superficial and deep venous network and the pattern of venous blood drainage within the foot. Elsner (2007) described the medial drainage of the plantar venous sinus which is fibrotically bound to the joint capsule. They found that this connection signifies a “toe-ankle pump” with a significant increase of venous blood flow during motion of the MTP joint. Based on this observation, they suggested the potential use of an external metatarsophalangeal (MTP) pump.

Binns (1988) dissected cadaveric feet to assess the function of the deep plantar veins as a “venous foot pump”. They found the lateral plantar vein to be larger than the medial and, more importantly, both of them to follow a convoluted and intramuscular course and to have valves facing proximally. They concluded that the deep plantar veins act as a pump that empties during contraction of the intrinsic foot muscles.

Corley (2010) contributed to further exploring the venous foot pump by describing the presence of a secondary deep plantar arch and deep connections in the foot along with patterns of doubling and dorsal connections of these veins. Less important and contributing compared to the previous, the foot or plantar venous pump propels blood towards the torso during foot movements.

To date, controversy exists over the exact mechanism of the venous foot pump. A review of the literature concerning the anatomy of the venous foot pump revealed that, though several studies have identified the lateral plantar vein, medial plantar vein, and deep plantar arch as the principal veins of the system, a lack of clarity exists over the naming conventions and detailed patterns of these veins.

Corley (2010) demonstrated, through his systematic dissections of the plantar aspect of 10 cadaveric feet, the presence of a previously unreported secondary deep plantar arch and/or deep connections in the foot. In addition, detailed patterns of doubling and dorsal connections were reported. A review of the physiology of the venous foot pump revealed that controversy exists over the role of weight bearing and muscular contraction for venous pumping in the foot. As it is difficult to determine the dominant mechanisms underlying the venous foot pump purely from anatomical dissection, further in-depth studies of the physiological aspects of the venous foot pump are required.

2.3.6 The valves

The superficial, deep and perforating veins contain internal valves that normally allow unidirectional blood flow from the periphery to the heart and from the superficial system to the deep. The function of these valves is passive responding with closure to retrograde blood flow and reverse pressure gradient.

The presence of one-way valves in the lower limb veins allows one to approach the venous network as an electronic circuit. Indeed, blood flow under normal circumstances is allowed towards a specific direction and always from the superficial system to the deep and from the periphery to the heart. This is a powerful and effective way to achieve blood return. Goldman 1989 explains that the presence of valves at regular intervals not only prevents blood reflux but also ensures that the intraluminal venous pressure is divided into “sub-columns” of blood in a vein.

2.3.7 The role of gravity

The lower limb veins are very compliant, which means that they can expand according to the amount of blood they contain and the respective intraluminal pressure that is applied to their wall. In an upright position, blood is pooled in the leg veins increasing the venous pressure. Certain physiologic mechanisms counteract the effect of gravity including the venous valves, the neurogenic (activation of the sympathetic system) vasoconstriction of the veins and the foot and calf muscle pumps.

Guyton (2015) describes that an adult who is standing perfectly still would have had a venous pressure of about +90 mmHg in their feet if it were not for the venous valves. Movement, in the form of walking, on the other hand, activates the calf muscle pump and a significant amount of blood is propelled towards the heart and the foot venous pressure decreases to +20 mmHg. In the case of standing still the gravitational venous pressure will reach again the value of +90mmHg in 30 seconds. This will have a domino effect on the pressure in the capillaries and eventually will lead to a fluid leak in the tissue spaces, causing oedema.

Without the operation of important compensatory mechanisms, standing upright would lead to significant oedema in the feet and lower legs in addition to orthostatic hypotension. Venous pooling and reduced venous return are rapidly compensated in a normal individual by neurogenic vasoconstriction of veins, the functioning of venous valves, by muscle pump activity, and by the abdominal-thoracic pump. Klabunde (2011) clarifies that when these mechanisms are operating, capillary and venous pressures in the feet will only be elevated by 10-20 mmHg, the mean aortic pressure will be maintained, and central venous pressure will be only slightly reduced.

When a person is lying down in a horizontal position, gravity is no longer causing a shift in blood volume from the thoracic compartment to the legs and feet. Klabunde (2011) explains that the thoracic (central venous) compartment has increased blood volume compared to standing. This increases preload on the heart, thereby increasing stroke volume, although the resulting increase in cardiac output will be tempered by a reduction in heart rate through vagal activation and sympathetic withdrawal. Sympathetic activation of the systemic vasculature is also reduced, which causes systemic vascular resistance to fall as the resistance vessels dilate. Henriksen (1991) described the veno-arterial reflex (VAR) and explained that sympathetic vasoconstrictor reflexes are essential for maintaining arterial blood pressure in an upright position.

2.4 Assessment of venous function

Assessment of the ability of the venous system to return the used blood to the heart involves a basic understanding of the relevant physiology and of basic fluid and human circulation applied dynamics.

2.4.1 Parameters and indices in assessing the lower limbs' venous return

Parameters include venous volume, 90% venous filling time, ejection volume and residual volume (Araki 1994).

2.4.1.1 Parameters

i. Venous Volume (VV) is the increment in volume of the calf that takes place when changing position from supine with the limb elevated to standing with the leg not touching the floor. It represents the venous blood volume that can be accommodated in the limb's veins.

ii. 90% Venous filling time (VFT90) is the time needed to achieve 90% of the venous volume and includes the time to shift from the supine position to standing up.

iii. Ejection volume (EV) is the amount of blood emptied from the calf with a single tiptoe manoeuvre.

iv. Residual volume (RV) is the amount of volume remaining in the calf immediately after a fast-performed series of 10 tiptoe manoeuvers. RV is not the difference between EV and VV. It is merely an estimate of the venous volume that cannot be shifted from the calf by exercise.

2.4.1.2 Indices

Indices, which include outflow fraction, venous filling index, ejection fraction, and residual volume fraction, are calculated by parameters and function as a means to provide comparable attributes between subjects.

i. Outflow fraction (OF) is the relative rate of calf vein emptying and is calculated as the percentage of calf volume that is expelled within 1 second after the release of a proximal occluding cuff. The patient is tested in the supine position with the leg elevated. The proximal cuff pressure is 80 mm Hg. OF is normal if greater than 40% (no evidence of outflow obstruction) (Back, 1995).

ii. Venous filling index (VFI) represents the average rate of increase in calf blood volume (ml/sec) between the supine position and standing. VFI is a combined measure of venous reflux and arterial inflow (VFI = 0.9 W/VFT90). Normal VFI is less than 2 ml/sec. in conjunction.

iii. Ejection fraction (EF) is the proportion of VV removed from the calf with a single, sustained tiptoe manoeuvre. EF estimates calf muscle pump efficiency as the percentage VV ejected by the calf with each contraction (EFp = [EV/VV] x 100). Normal EF is 60% or greater.

iv. Residual volume fraction (RVF) is an estimate of the dependent leg fluid volume that cannot be extracted by exercise (10 tiptoe movements). RVF = (RV/VV) x 100. Normal RVF is less than 35%.

2.5 Stroke Distance – Lessons learned from Doppler Echocardiography

The musculo-venous pump of the calf has been described as the peripheral “heart” for the venous part of the circulation. Araki (1994) assessed ulcerated lower limbs’ venous haemodynamic parameters and indices by using air plethysmography to show that, although venous insufficiency is necessary to cause ulceration, a deficiency of the calf muscle pump is significant to the severity of the pathology. Simka (2004), using similar techniques, found a direct correlation of calf muscle pump deficiency and the extent of the leg ulceration. Both researchers used the calf pump’s ejection fraction as their primary outcome variable. Williams (2014) revisits the calf muscle pump and reports that failure of the peripheral pump and hence reduction of the ejection fraction occur in cases of musculofascial weakness, loss of joint motion, valvular failure of outflow obstruction.

Ejection fraction of the left ventricle (LVEF) is a recognized indicator of prognosis in patients with heart failure. Curtis (2003), investigating its importance showed a linear increase in mortality for LVEF less than 45%. For a healthy human calf the venous ejection fraction is expected to be approximately 65%

The calf muscle pump has been described as an analogy of the heart in terms of both function and importance in circulation. Indeed, contraction of the calf muscles results in the propulsion of the blood in the deep veins cephalad (ie towards the torso). The vein valves prevent flow towards the opposite direction just like the heart valves do. The chamber of the human heart responsible for the arterial part of the systemic circulation is the left ventricle and its assessment in case of heart failure is of paramount clinical importance.

Echocardiography is considered to be the gold standard non-invasive assessment technique of left ventricular function. This is an ultrasound-based examination and measurement of a number of haemodynamic parameters, such as blood flow velocities, ejection fraction, and stroke volume. In the majority of literature and in current clinical practice the function of the left ventricle is measured and expressed as its ejection fraction.

Haites (1985) measured aortic stroke distance in 140 healthy adults and concluded that it is a safe, simple and physiologically valid assessment for cardiac function comparable to ejection fraction, stroke volume and cardiac output as indices of left ventricular systolic function. Singer (1993) describes the characteristics of aortic outlet waveforms taken through esophageal Doppler devices in an analytical review of esophageal monitoring of aortic blood flow. The velocity – time waveform in real time is analyzed in terms of shape, peak, frequency, and area under the curve. The area under the velocity vs time curve is defined as Stroke Distance (SD) or Velocity-Time Integral (VTI) (measured through TAV – Transcutaneous Aorto Velography - with Duplex scanners). (Fig 2.13).

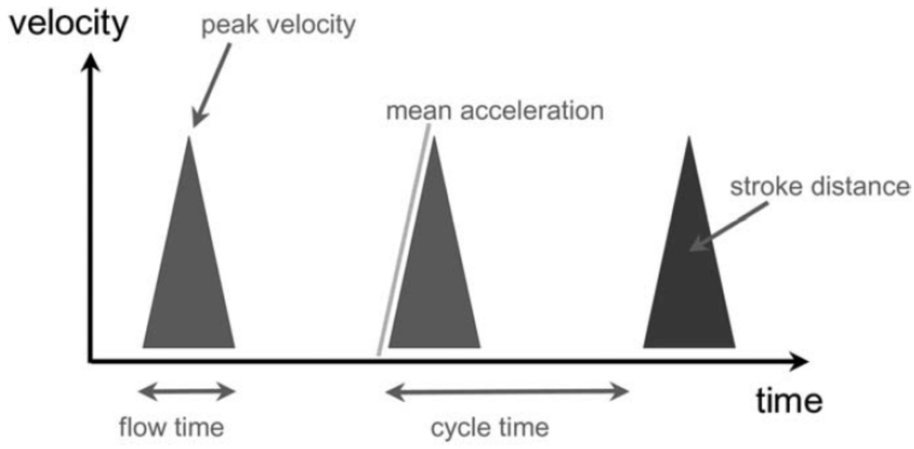


Figure 2.13: Velocity/time graph. The area under the curve is the Velocity Time Integral (VTI), also referred to as Stroke Distance (SD)

Trent (1999) points out that, although echocardiography seems to be a useful tool in assessing patients with heart disease, infrequently, some of these patients are “non-echogenic”, meaning that the test can be difficult to perform and interpret. In their work, they used a different parameter, known as systolic velocity integral of blood flow or stroke distance, also referred by many as velocity-time integral. In a sample of 378 patients with a history of myocardial infarction, they established a measurement of the stroke distance as a reliable index for differentiating high and low-risk patients with a predictive accuracy comparable to that published for the left ventricular ejection fraction.

Goldman (2000) showed that stroke distance is independent of left ventricular outflow area (the cross-sectional area at the origin of the aorta) and can be used directly as a left ventricle function index in its own right. Firstenberg (2000) explains that stroke distance reflects from a physiologic point of view the work of the left ventricle against the afterload and, in cases of valvular regurgitation, it is superior to ejection fraction.

Velocity-Time Integral (VTI) (or Stroke Distance) is widely described as the “area under the curve” (AUC) in a graph of velocity versus time. It is the integral of all velocities during the time of flow through a vessel. During this period a Doppler device will calculate blood velocities along its scan range line. These velocities are plotted against time and the area under the velocity-time curve is calculated using Fast Fourier Transformation. VTI, strictly speaking, is measured in length units (cm) as is the product of velocity multiplied by time. In that sense, it implies the “distance traveled” by an amount of blood (e.g. a red cell) traveling with the calculated velocity.

Alternatively, another way to visualize this is a number of blood cells traveling with different to each other velocities (as the graph curves describe) over a certain period of time. This latter analogy might be closer to really take place in a vessel as the flow can be and usually is chaotic with different layers of blood moving with different speeds, areas of turbulence and acceleration.

2.6 Assessment modalities of the venous circulation

2.6.1 Non-invasive techniques

Several techniques of measuring and assessing the blood flow have been described and evolved following the progress of technology. Duplex ultrasonography is considered to beat the golden standard of venous flow assessment. Other techniques have a place, depending on the particular research or clinical diagnostic questions; these include ultrasound Doppler velocimetry, duplex ultrasonography, photoplethysmography, laser Doppler flowmetry, air plethysmography, strain gauge plethysmography and transcutaneous oxygen (TcPO2) measurement.

2.6.1.1 Ultrasound Doppler Velocimetry

The Doppler ultrasound technique uses the Doppler Effect or frequency shift to assess the direction and velocity of blood flow. A suitable probe is placed over the vessel to be examined and the ultrasonic signal emitted is analysed on its return. Thomson (2001) explains that a handheld Doppler device can carry out a simple assessment of venous reflux and it should be a part of the routine assessment of patients with venous disease.

2.6.1.2 Duplex Ultrasonography

Duplex ultrasound is widely regarded as the method of choice when it comes to non-invasive assessment the functional capacity of the lower limb veins. It combines color flow imaging with B-mode (a form of two-dimensional ultrasound that allows visualization of the tissues) and pulsed Doppler which tests blood velocity. This combination allows both visual and haemodynamic assessment of the examined vessel. It is a simple test to perform, cost-effective, reliable and fast method to evaluate the anatomical and functional status of a vein. Nicolaides (2000) in a consensus statement describes the technique and the significance of findings of Duplex scanning of the lower limb veins.

2.6.1.3 Photoplethysmography

Photoplethysmography (PPG) is a complex and technically demanding method which utilises light emission and measures changes in light absorption. It indirectly estimates the venous return by measuring the filling of the small skin veins using a photometric technique. Nicolaides (2000), points out that a venous refill time of fewer than 20 seconds, in a standing patient is suggestive of Chronic Venous Insufficiency (CVI).

Eberhardt (2005), states that PPG can provide a general assessment of the physiological status of the venous system and it is very sensitive in tracing the venous disease.

2.6.1.4 Laser Doppler Fluxmetry

Samik (2007) explains that Laser Doppler Flowmetry (LDF) is a sensitive non-invasive method of assessment of the superficial skin perfusion and, consequently, the perfusion of the part of the body examined. It has been used for monitoring variations in the cutaneous peripheral microcirculation. It uses a monochromatic low-energy laser beam which enters the tissues and is reflected and recorded by a sensor. It is subsequently analysed in a way similar to the Doppler Effect ones. The LDF devices are large and heavy devices. Even portable LDF is too large to be attached to a mobile patient. They are typically used for detection of deterioration of the skin’s microcirculation after operations incorporating complex skin grafts.

2.6.1.5 Calibrated Air Plethysmography

Air plethysmography is a method of assessment of changes in the volume of the anatomic area examined. In the case of the lower limb, a pneumatic cuff is wrapped around it and the participant is placed in different body position that would encourage the venous blood flow from and toward the leg. Air plethysmography is sensitive enough to assess venous reflux (venous flow towards the foot), venous occlusion and inefficient calf muscle pump mechanism. Changes in calf volume are measured by air displacement (Eberhardt, 2005).

Calibrated Air Plethysmography was conceptually originated at St Mary's Hospital, London by Nicolaides (1993) and is able to make a number of haemodynamic measurements including: the volumetric rate of reflux, venous volume in the calf, calf muscle pump function expressed as ejection fraction, chronic deep vein obstruction, and arterial inflow rate.

Christopoulos (1987) showed that air-plethysmography is not only a diagnostic tool but it also offers a unique technique to assess the haemodynamic effects of elastic compression.

Although a non-invasive and accurate test (Eberhardt 2005), the testing protocol is quite complex and impractical and is not ideal for real-time tracking of sudden changes of blood flow when intermittent pneumatic compression is applied on the leg.

2.6.1.6 Strain gauge plethysmography

Strain gauge plethysmography uses a circumferential wire or tape encircling the upper calf connected to a large device that is very sensitive to changes of the size of the calf. During certain maneuvers the perimeter of the calf is proportional to the amount of the blood it contains. As the main volume of blood occupying the lower leg's vessels is venous, the changes in size reflect the capacity and function of the lower limb's veins. This method, although sensitive is impractical to be used in association with IPC. Englund (1971) assessed the validity of the method by altering the regional perfusion of a human limb and found a linear relationship between inflow and the plethysmographic recorded flow.

2.6.1.7 Transcutaneous oxygen (TcPO2) measurement

Transcutaneous oxygen tension (TcPO2) measures the partial pressure of oxygen at the skin surface, using a heated electrode. It is a slow and time-consuming method, both, to set up and to collect data.

Kolari (1988) measured the TcPO2 near the edge of venous ulcers before and after application of 60 minutes of Intermittent Pneumatic Compression. He found a highly significant increase of TcPO2 following IPC correlating with reduction of oedema and inverse change of skin temperature.

2.6.2 Invasive Techniques

2.6.2.1 Phlebography

Phlebography is an invasive method and involves the injection of contrast into the examined vein and subsequent radiological studies (series of x-rays). It is highly accurate in diagnosing mostly anatomic abnormalities and for a number of years, it was the gold standard for the anatomical assessment of venous insufficiency. Phlebography can be ascending (contrast injection into a vein of the dorsum of the foot) or descending (injection of contrast through a cannula into a more proximal vein – femoral/popliteal/brachial). Nicolaides (2000) described both methods and explained that although phlebography has been the gold standard in the anatomical identification of venous obstruction, it cannot provide information on the functional status of the venous system.

2.6.2.2 Ambulatory Venous Pressure

Ambulatory venous pressure (AVP) monitoring is a sensitive invasive technique of assessing venous pressures before during and following leg exercise. A needle is inserted into a superficial foot vein and connected to a pressure transducer. A combination of ten tip toe maneuvers and cuff placement (to temporarily obstruct the flow in the superficial veins) provides an accurate assessment of the haemodynamic status of the leg veins (Nicolaides, 1993).

2.7 Pathophysiology of venous ulceration

Venous ulcers are the most dramatic and difficult to treat final clinical manifestation of chronic venous insufficiency. Ulcers are skin erosions and, in the case of lower limbs, affect almost exclusively the lower calf or the foot. They are the end result of long standing superficial and deep chronic venous insufficiency, post-thrombotic syndrome, and venous stasis.

It is widely accepted that the dominant force in the pathophysiology of lower limb ulceration is chronic venous hypertension. Bergan (2006), explains that the exact pathophysiologic mechanisms, however, are widely disputed and proposed theories, describing fibrin cuff formation and growth factor trapping, have failed to gain widespread support. One of the most popular theories, the white-cell trapping hypothesis of Coleridge-Smith (1988), is a great attempt to provide a complete explanation to the phenomenon.

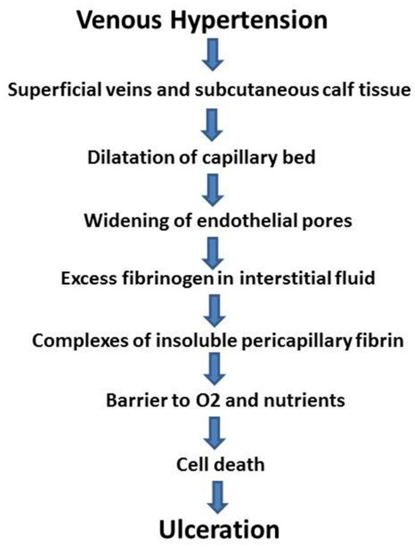


Figure 2.14: Depiction of Coleridge Smith et al's theory for the pathogenesis of venous ulcers

2.7.1 Venous stasis

Venous stasis is the condition where the blood flow in the veins (most commonly the lower limbs) is very low. It is one of the predisposing factors for the formation of venous thrombi – the other two being hypercoagulability and endothelial injury (Virchow 1821-1902).

Manjit (2008), while measuring the serum and wound cytokine levels of patients with venous ulcerations, found that wound fluid collection volume correlates with ulcer size. The finding is in accordance with the common belief that lower limb oedema is related to venous ulcers even when there is no evidence of obvious venous insufficiency.

The term chronic venous insufficiency (CVI) covers a wide range of pathologic conditions whose origin and the common denominator is venous blood stagnation and its aetiology varies. Chronic venous insufficiency can affect the superficial or deep venous systems or the perforating veins connecting them.

2.7.2 Superficial chronic venous insufficiency

By far the most common form of CVI, superficial chronic venous insufficiency is a failure of the superficial system to drain the containing amount of blood effectively to the deep system. In its commonest form - venous hypertension due to reflux in the superficial venous system - has a prevalence of 1% to 73% in females and 2% to 56% in males (Beebe-Dimmer 2005). In the majority of the cases, this dysfunction of valves in the superficial and/or communicating veins is due to congenital or acquired incompetence (Valencia 2001). Varicose veins are tortuous, widened, elongated veins in the subcutaneous tissue of the lower limb (Cambell 2006). As long as the venous insufficiency is limited in the superficial venous system, it can be treated with surgical (removal/ligation of the incompetent veins) or interventional (endovenous obliteration) methods. For symptomatic patients where surgical or interventional treatments are not an option; the alternative is conservative treatment in the form of compression.

2.7.3 Deep chronic venous insufficiency

The clinical presentation of deep venous insufficiency is more dramatic and difficult to treat, both conservatively and surgically. Invariably, combined with superficial venous insufficiency, deep CVI is caused by non-functional refluxing valves or venous obstruction which is most commonly a consequence of deep venous thrombosis (Nicolaides 2000 and Alguire 1997).

2.7.4 Deep venous thrombosis

The formation of thrombi in the vessels of the deep venous system can be caused by various factors whose common denominator is the triad of Virchow: a combination of hypercoagulability, haemodynamic disturbances (stasis, turbulence) and endothelial dysfunction. The clinical presentation can vary from silent to limb and/or life threatening depending on the localization and extent of the thrombosis (Di Nisio 2016). The acute syndrome can be treated conservatively, interventionally or surgically. None of these treatments, however, can guarantee complete dissolution of the thrombi, especially the ones lodged on the valves. The chronic presence of clots in the valve pockets will eventually lead to their scarring, incomplete closure and venous hypertension.

2.7.5 Post thrombotic syndrome

Post-thrombotic syndrome (PTS) is a term used to describe a constellation of symptoms and signs that follow one or more episodes of deep venous thrombosis characterized by chronic pain, discomfort, and progressive skin changes. Untreated, it will invariably lead to severe skin atrophy, discoloration and lipodermatosclerosis, skin hyperemia and eventually ulceration. PTS typically initiates years following the original event and is classically treated with compression.

2.7.6 The role of oedema

The presence of oedema in the above-described conditions is a common denominator and is observed in all cases of venous ulceration. The currently accepted pathophysiologic theory around venous ulceration considers oedema as part of the process. Venous obstruction (DVT) and a venous incompetence (valvular incompetence) increase of the venous hydrostatic pressure. The lymphatic system fails to drain the accumulating interstitial fluid and the limb appears edematous, particularly at the end of the day. The presence of fluid in the tissues changes the shape of the leg, making the application of compression hosiery an even more difficult task and creating a disturbing and depressing body image. A large number of patients with venous insufficiency are referred for further assessment, with only leg oedema as their single original complaint.

Grieveson (2003) conducted a study to examine the degree of the oedema reduction when using an IPC device. They concluded, albeit using a single chamber device that moderate levels of compression (30-40 mmHg) successfully reduced the amount of leg oedema.

2.8 People at higher risk

The incidence of the venous disease in developing countries is similar to that in Western countries, making this a universal phenomenon that spares no geographical or racial limits.

Rabe (2010) demonstrated by analysing The Bonn Vein Study that risk factors for venous disease progression were increasing age, obesity, and arterial hypertension

The incidence of venous leg ulcers in the population is 0.76 (0.71-0.83) for men and 1.42 (1.35-1.48) for women per 100 person years (Margolis 2014). Berliner 2002 showed that leg venous ulcers affect 0.18-1.3% of adults. The rate of complete healing in the first 4 months was only 50% of patients, 20% in 2 years, and 8% in 5 years after the start of venous ulcers.

2.8.1 Age

Various studies have shown the slightly different incidence of the condition, all of them, however, agree that the incidence increases with age. Callam (1985) pointed out that leg ulceration is, not only a problem for the elderly but also affects younger people, often resulting in substantial loss of working time. The proportion of people with leg ulcers is just less than 1% of people under the age of 60, 2.6% for people between 61 and 70 and 15% for people over the age of 80 (Nelson 2011). In the steadily aging of the population of the western world, venous ulcer disease takes epidemic dimensions. Elderly people are more prone to develop ulcers because of poor mobility and possibly skin atrophy.

2.8.2 Gender

Although the onset of leg ulceration in females and males under 30 years of age is similar, after that age the female-to-male ratio becomes 2:1 and after the age of 80 1.7:1 (Abbade 2005). A possible explanation could be differences in hormonal and pregnancy-related factors, although geographical ones cannot be excluded. Venous ulcers are most common in females with ratios ranging from 1.5:1.5 to 3:1 depending on the survey (Callam, 1985).

Callam (1985) reported that 87% of the patients with venous ulcers were managed by a primary care team (built around General Practice) and only 13% in a Hospital. With an estimated 1% incidence in the UK, there is a population with leg ulcers of roughly 600,000. With a moderate current estimation, 80% (480,000) of those are treated in the community. This is where this project could be a game changer with the ultimately extensive use of an advanced technology, patient-friendly IPC device that can be used, not only in a healthcare setting but also at home.

2.8.3 Body weight

Benigni (1992) found that 25% of patients with venous ulcers were obese and that the duration of the ulcer in this population was significantly longer compared to the non-obese sample. They showed that popliteal vein reflux is more frequent in obese patients and the symptoms of paresthesia and pruritus that are commonly associated with active venous ulcers, were more severe in patients with high Body Mass Index (BMI). Milic (2009) found that a BMI higher than 33 was associated with delayed venous ulcer healing.

2.8.4 Mobility

People who are unable to walk or with poor mobility have a greater chance of developing significant lower leg skin changes and ulcers (Abadi 2007). A short walking distance covered during the day of fewer than 200 metres is associated with slow venous ulcer healing (Milic 2009). Investigation of the relationship between clinical severity of venous disease, calf muscle pump dysfunction, and range of ankle movements showed a reduced range of ankle movements in patients with primary varicose veins was inversely proportional to the severity of venous disease (Dix 2003).

2.8.5 Medical Conditions

A number of medical conditions have been associated with venous leg ulcers. As people with advanced age have a greater propensity to develop leg ulcers, it is expected that a number of medical conditions commonly observed in old age would be connected to them. Indeed, a number of medical pathologies have been found to be linked to active venous ulcers. Margolis (2004) explains that asthma, cellulitis of the lower extremity, congestive heart failure, diabetes, deep venous thrombosis, lower limb oedema, osteoarthritis, peripheral vascular arterial disease of the lower extremity, rheumatoid arthritis, history of hip surgery and history of venous surgery / ligation have been shown to be significantly associated with the onset of a new ulcer.

Among these conditions is a history of venous surgery, which is supposed to be a form of treatment for chronic venous insufficiency with the goal of ultimately preventing the formation of an ulcer. In addition, research has shown that several medical conditions are negatively associated with or protect patients from venous ulcer formation such as angina, cerebral vascular accident, depression, malignancy, myocardial infarction, pneumonia and urinary tract infection (Margolis 2004).

2.8.6 Lifestyle and socioeconomic factors

It has been shown that longer duration of ulceration is associated with the lower social class (Callam, 1985). Lack of central heating has a strong association with prolonging healing of venous ulceration (Franks, 1995).

2.9 Venous ulcers

Venous ulcers are the final and most striking manifestation of venous hypertension. Up until their presentation, patients’ symptoms are either minimal or easily manageable. The onset of a new ulcer is followed by a dramatic change of lifestyle and a sudden drop in quality of life.

2.9.1 Clinical presentation

The natural history of venous ulceration is that of a gradual, chronic progression of skin changes typically affecting the lower third of the calf. The initial discoloration in the majority of the cases appears in the anteromedial aspect of the distal calf but it eventually spreads in a circumferential way to encircle it. The change in skin colour is accompanied by hardening and tightness of the skin, a type of chronic inflammation called lipodermatosclerosis and gives the calf a shape of the inverted champagne bottle.

The first signs of ulcerations follow this stage and originally appear as small, superficial skin breakdowns that are either single and increase in size eccentrically or multiple and tend to eventually unite to form larger ones. In the early stages of ulceration, the lesions are superficial and produce a moderate amount of clear fluid called exudate. The amount of fluid discharge follows the ulcer's changes of dimensions and is considered as another sign of venous hypertension. The exudate is characterised by an unpleasant odour that typically penetrates even the tightest and most absorbent types of dressings and bandages and, thus, seriously affects the patients' quality of life.

2.9.2 Quality of life

Quantitative studies commonly investigated the parameters of pain, sleep, social isolation, and physical mobility. Patients had significantly more pain, more restrictions regarding social functioning, less vitality, and limitations with respect to emotional roles compared to the respective controls (Herber, 2007).

Up to 97% of patients with ulcers appear to have limitations to their physical functioning, affected family life and are dependent on members of family or partners in terms of care provision. Social life is restricted by pain, bandage appearance, odour and inability to dress appropriately (Green, 2010)

2.10 Forms of Compression

Laplace's Law

The law of Laplace states that the intracavitary pressure (*P*ic), more precisely the difference between the external pressure (which frequently is ignored as being constant and is usually equal to the atmospheric pressure), is directly proportional to the wall stress (*W*s) and inversely proportional to the equivalent radius.

2.10.1 Static Compression

Early in the history of treatment of chronic venous insufficiency, venous stasis, venous hypertension and their clinical complications, it was realised that the simplest way to reverse the causing factors and alleviate the symptoms was to apply external compression to the affected limb. The first form of compression ever applied was circumferential bandages that served three purposes: compression, fluid absorption, and discretion by keeping the ulcers well covered. Unfortunately, these practices have changed very little over the centuries, with some improvements in the types of the bandages and their ability to effectively provide to patients the aforementioned triad.

2.10.1.1 Compression Bandages

In most clinical institutions the general treatment provided for venous leg ulcers is compression bandaging. Generally, a health professional will dress the ulcerated limb every week or more frequently, depending on the stage and fluid discharge of the ulcer. The ulcer is cleaned with normal tap water/saline/antiseptic solution and dressed. When not dressed in the right manner, may lead to infection and further deterioration of the ulcer in terms of its extent and depth.

Compression therapy is widely used in the treatment of venous leg ulcers but this is not necessarily based on the amount of evidence available to justify the practice. A systematic review from Palfreyman (1998) showed that there is a statistically clear benefit from elastic and multi-layer systems in terms of the number of ulcers healed. However, there is only one trial within each comparison and so the results cannot be said to be conclusive.

2.10.1.2 Compression stockings

Compression hosiery comes in different sizes, lengths and applied compression profiles to fit patients with different leg sizes, the extent of venous insufficiency and severity of the problem respectively. Although it can be a personalised solution to a degree, and although it is today by far the commonest way of compression in all manifestations of venous disease, there are some areas of weakness. There is poor patient compliance as a result of the discomfort compression stockings cause (Berliner 2003).

Nicolaides (2016) explains that the main mechanisms of action of compression are: reduction of oedema, enhancement of the ejection fraction, decrease of venous reflux and restoration of the veno – arterial reflex.

There is however large individual variability of the deep veins response to compression stockings, a fact that suggests that the hosiery selection process has to be more individualised to the patients' needs (Wang 2012). In other words, despite the availability of a range of sizes and compression profiles, compression stockings fail to ensure patient-specific, effective, predictable compression.

2.10.2 Dynamic Compression

Disappointing long-term outcomes, lack of patient compliance and the accelerated progress in technology support exploring alternative compression treatments. Dynamic compression has the advantage of mimicking the physiological dynamic pumps of the human foot and calf. Also, by definition, it does not compress the lower limb continuously, making it more tolerable compared to bandages and stockings.

2.11 Alternatives to Compression

Patients, who cannot tolerate compression nor have relative contraindications to it (e.g. co-existing arterial disease), will need an alternative form of treatment, limited to elevation, neuromuscular stimulation, surgical treatment and Intermittent Pneumatic Compression (IPC).

2.11.1. Elevation

The elevation is the first and simplest method of alleviating CVI symptoms. Ideally, the affected limb or limbs should be elevated above the right atrium's level. As a large number of patients suffering symptomatic CVI are elderly with co-existing medical conditions such as cardiac failure or arthritis, the elevation at such a high level is sometimes uncomfortable or even impossible.

2.11.2 Neuromuscular Stimulation

Neuromuscular Stimulation (NMS) is a promising field with a growing research interest. It refers to the application of low amplitude current through special skin-adherent electrodes to muscles or nerves that innervate the muscles in question. Haemodynamic studies of the peak systolic velocities in the popliteal vein during and soon after NMS of the gastrocnemius muscle showed significant flow augmentation (Clarke-Moloney 2006).

2.11.3 Surgical Treatment

Although surgical and interventional treatments have a place in superficial chronic venous insufficiency, the results of surgery in deep venous insufficiency have generally been disappointing. Procedures, such as neo-valve formation, vein interposition grafts, and venous bypasses, are only performed to avoid amputations. In cases of venous obstruction bypass surgery can be a viable option for large size veins (Gloviczki 1992) but the results in medium and small size veins are disappointing. Stenting of the above the inguinal ligament veins has been used for chronic iliac vein obstruction but the quality of evidence to support the use of deep venous stenting for this pathology is currently weak (Seager 2016). This leaves a wide range and a large number of patients with significant symptoms and extensive ulcers that still need to be treated conservatively (Raju, 2008).

2.12 Intermittent Pneumatic Compression

Chronic venous insufficiency causes venous stasis, venous hypertension (increased blood pressure in the veins) and oedema of the legs. The above can eventually lead to skin changes and ulceration. Application of local pressure has been found to stop and reverse these effects by changing the pressure gradient in the tissues, thus reducing oedema and the vein calibre and, hence, the intravenous pressure by increasing the effectiveness of the muscle pump. Venous insufficiency is no longer sufficient, to cause ulceration (Araki,1994).

Pneumatic Compression therapy is one of the largest and fastest expanding markets in the medical field worldwide. In a 2012 survey (ASD Reports, 2012), this market was estimated to be above $1.1 billion. The growth rate was found to be 5% every year, which will result to $2.8 billion by 2018. This market survey was conducted on all type of compressive products (i.e. compression bandages, stockings and Pneumatic Compression Devices). The reason for such a high demand and popularity for these products is due to the increased aging population and the flexibility of these products to treat different kinds of illness.

Mechanisms of action

The effect of IPC upon the venous circulatory system incorporates a combination of mechanical, haematological and biochemical factors that combine to create the physiological equivalent of motion without moving. The increase of blood flow in the veins, the positive effect on the fibrinolytic activity and the reduction of the subcutaneous oedema are phenomena observed during active exercise as well.

2.12.2 Haemodynamic effects

Venous flow augmentation, the increase of blood flow in the veins during and after application of IPC, is a well-acknowledged haemodynamic effect. Studies have been performed checking the changes of velocity and/or flow at different anatomical levels and with no exception have confirmed positive flow response to intermittent pneumatic compression.

Three mechanisms have been postulated to explain the augmentation of flow with IPC:

1. An increase in the arteriovenous pressure gradient with a decrease of venous pressure

2. The production of endothelial vasodilators in response to the increase in shear stress and

3. The suspension of peripheral sympathetic autoregulation (veno-arteriolar response) with the decrease of venous pressure (Delis 2001 and 2005).

Flam (1996) showed that average flow augmentation, which is a direct measure of the amount of femoral vein blood flow velocity increases over the base, was 107% +/- 49% with a knee-high system, and 77% +/- 35% with a thigh-high IPC system (P <0.002). Augmentation was higher for 62% of the subjects with knee-high IPC, and for 23% of the subjects with the thigh-high system. Overall, the blood was actively moving through the vein during the decompression phase. On occasion, the velocity during the decompression phase would fall to zero for short intervals with both systems, indicating complete emptying of the vessel.

2.12.3 Hematologic effects

Fibrinolysis is a normal, physiological process of which the human body controls the formation of thrombi. For example, a primary protective thrombus will form on the site of injured venous endothelium. The extent of the thrombus formed and its final breakdown is controlled with fibrinolysis. The most significant non-haemodynamic effect of IPC is its fibrinolytic activity.

Fibrinolysis is the normal physiologic response of degradation of newly-formed intravascular thrombi. Through a complex physiologic mechanism, the endogenous fibrinolytic system balances the production (e.g. in the case of vessel wall injury) and degradation (lysis) in the case of abnormally produced thrombus (e.g. deep venous thrombosis). Several researchers have demonstrated that IPC enhances fibrinolysis (Comerota, 1997 and Allenby, 1973). Hoppeensteadt (1995) studied extensively the role of Tissue Factor Pathway Inhibitor (TFPI), an important anticoagulation peptide, and Jacobs 1995 form the same team demonstrated that intermittent pneumatic compression induces short-lived but prompt changes in both haemodynamic and fibrinolytic functions.

Effects on endothelial cells of intermittent flow and vessel collapse, either individually or simultaneously, were simulated with a new in vitro system. Original tests of that system showed that intermittent flow, associated with intermittent pneumatic compression, upregulates endothelial cell fibrinolytic potential and influences factors altering vasomotor tone (Guohao 2000). Furthermore, another team showed that irrespective of the type of device or form of IPC, the elevation of fibrinolytic activity was dramatic at 180 minutes in normal subjects and post-thrombotic patients (Comerota, 1997).

2.12.4 Effects on oxygen tension

The transcutaneous oxygen measurement is a technique that assesses the skin's oxygenation, in a non-invasive manner. Although the exact pathophysiologic mechanism behind the progressive skin destruction in chronic venous insufficiency is unclear, it is believed that the stage before the onset of skin ulcerations is characterised by impaired oxygen supply to the subcutaneous tissues. Interestingly, the oxygen content of the venous blood in affected limbs is increased, a phenomenon that has been explained as a result of arterio-venous shunting at the level of the capillaries. This results to increased oxygen pressure in the dermis and decreased pressure in the superficial capillaries (Malanin 1999).

2.13 Indications for Intermittent Pneumatic Compression (IPC)

2.13.1 IPC for venous ulcers

Although the original IPC devices were not designed for application on patients with venous ulcers, it soon became obvious that periodic external compression could achieve the same early effects (reduction of oedema and ulcer fluid discharge) as the traditional compression bandages and stockings. Elimination of oedema is considered essential as it causes redistribution of skin blood flow in the lower limbs, improving the superficial capillary perfusion (Malanin 2009). The advantage over static bandages is that the compression applied is not continuous and, hence, the use of IPC is much better tolerated which makes patients ultimately, more compliant.

2.13.2 IPC for arterial disease

Mokhtar (2008) investigated the effects of foot and calf IPC on healthy subjects' popliteal artery's peak systolic flow and found that the latter increased (mean increase 15%) and the effect lasted for at least 10 minutes after the end of IPC.

In patients with mixed ulceration, an ankle-brachial pressure index > 0.5 and an absolute ankle pressure of > 60 mm Hg, inelastic compression of up to 40 mm Hg does not impede arterial perfusion but may lead to a normalization of the highly reduced venous pumping function. Such bandages are therefore recommended in combination with walking exercises as the basic conservative management for patients with mixed leg ulcers. (Mosti, 2012). IPC, by augmenting leg perfusion, achieved improvement in walking distance comparable with supervised exercise.

Intermittent pneumatic foot compression used at home for 4.5 months increases claudication distance by over 100%. Associated significant increases Ankle – Brachial Index (ABI), and arterial calf inflow suggest an improved collateral circulation. The maximum benefit seems to be offered over the initial 3 months. Treatment benefits are maintained 1 year after treatment. A multicentre study is indicated to quantify actual benefits and to demonstrate cost effectiveness (Delis, 2000).

Ramaswami (2005) found that IPC improves walking distance in patients with stable intermittent claudication and alleviates symptoms of limb ischemia. Also, IPC should be the first treatment modality in patients with disabling claudication who are unfit for major reconstructive surgery.

This study has shown a significant increase in popliteal artery mean systolic flow in patients with intermittent claudication after the application of IPC to the foot and calf. There was also a reduction in popliteal artery mean systolic flow from the supine to sitting and to the standing position.

2.13.3 IPC for lymphoedema

Lymphoedema, either primary (not associated with an existing disease) or, most commonly, secondary (as a result of previous operation/infection/or trauma/malignancy) results from the inability of the lymph vessels to drain the interstitial fluid back to the main circulation (Ridner 2013). Patients suffer grossly oedematous limbs. Treatment of choice is conservative and consists of external compression. Sequential Intermittent Pneumatic Compression (SIPC) is an established method for treatment of peripheral lymphoedema (Richmand 1985 and Pappas 1992). Dennis (1993) demonstrated that not only IPC for lymphoedema is important but also early application achieves better clinical outcomes. Generally lymphoedema – targeting IPC devices (eg Lymphapress) use longer compression cycles and higher compression pressures compared to the venous disease orientated devices (Johasson 1998).

2.13.4 IPC for prevention of DVT

Deep venous thrombosis is a serious potentially fatal and often debilitating in the long run condition. It is usually associated with long periods of immobilisation typically following long surgical procedures. The combination of blood stagnation in the lower limb veins, the increased viscosity (associated with dehydration/fluid imbalance) and micro injuries of the venous endothelium consist the triad of Virchow and predispose to formation of thrombi in the deep veins of the lower limbs.

These thrombi can travel and end up occluding vital vessels in the lungs (pulmonary embolism) or remain attached to the vein lumen, where, eventually, they cause permanent malfunction of the vein valves. Even when, occasionally, the central part of the thrombus degrades to allow recanalization of the occluded vessel, the valves sustain permanent fibrosis that results in their inadequate closure and subsequent reflux.

Several methods to avoid all the above have been developed: early patient mobilisation, administration of anticoagulants (heparin), compression hosiery and intermittent pneumatic compression devices. The latter can be used intraoperatively (during the surgical procedure) and postoperatively in combination with one or more of the other methods.

2.13.5 IPC and sports

Intermittent Pneumatic Compression devices dedicated to sports recovery already exist commercially. Zelikovski (1993) showed that application of IPC after a training session resulted in 45% improvement in the participants' ability to perform a subsequent exercise bout. Although the literature supporting this indication is limited, there are commercially available devices to serve this purpose.

2.14 IPC devices

2.14.1 Early forms

Large in size and heavy, the first IPC devices looked like crude prototypes of their most recent descendants. The original trend was that of treating patients during clinic visits on bi- or tri- weekly sessions and, hence, the size of the devices did not matter. Miniaturisation, use of lighter sleeves and single use sleeves followed along with attempts to develop feedback mechanisms (Murakami 2003, Ben-Galim 2004).

The spreading use in DVT prophylaxis created user-friendly devices, however, with a limited number of function modes and pressures. Their function parameters were invariably based on limited research and, in some cases, long-lasting dogmas. An example was the first ever tested on patients IPC device with an attempt to improve the arterial supply. Ironically, a generation of devices that followed it aiming treatment of venous disease or lymphoedema, contraindicated their use in patients with coexisting arterial disease

2.14.2 Modern IPC devices

A variety of IPC devices today target, not only venous ulcer treatment but also the vast area of DVT prophylaxis, a market even larger and rapidly expanding. Commercial IPC devices vary greatly in terms of their physical and functional characteristics and their haemodynamic effects to the lower limb's venous circulation. Proctor (2001) compared five devices and reported significant differences in peak systolic velocity, mean systolic velocity, and peak volume flow in normal volunteers.

There are 3 basic types of IPC devices:

i. A non-segmented pneumatic compressor is a device which has a single outflow port on the compressor. This outflow port is connected to a single chamber sleeve/appliance and may achieve a sequential pressure gradient through the design of the tubing and/or air chambers in the sleeve/appliance (Hoover 2009).

ii. A segmented pneumatic compressor without calibrated gradient pressure is a device which has multiple outflow ports on the compressor that leads to distinct segments on the appliance which inflate sequentially. These devices achieve sequential compression by either (a) application of the same pressure in each segment or (b) application of a predetermined pressure gradient in successive segments but no ability to individually set or adjust pressures in each of one or several segments. In these devices, the pressure is usually set by a single control on the distal segment. They are used with sleeves/appliances that are multichambered, thus allowing for sequential, gradient compression (Hoover 2009).

iii. A segmented device with calibrated gradient pressure is characterized by a manual control on at least three outflow ports which can deliver an individually determined pressure to each segmental unit. These IPC devices are also used with a multi-chambered sleeve/appliance to achieve sequential, gradient compression (Hoover 2009).

2.14.3 Variability of technical characteristics

Although there are a significant number of IPC devices on the market, none of them offer full control of their function to the clinicians or patients who use them. The range of pressures is variable and most commonly dictated by safety measures. Hence, according to their target pressure settings, there are two main categories: low-pressure devices indicated for venous or arterial disease operating at pressures not generally exceeding a maximum pressure of 150mmHg (using short-duration compression cycles) and devices for symptomatic treatment of lymphoedema using significantly higher pressures up to 250 mmHg (over long duration cycles) (Fig 2.15).

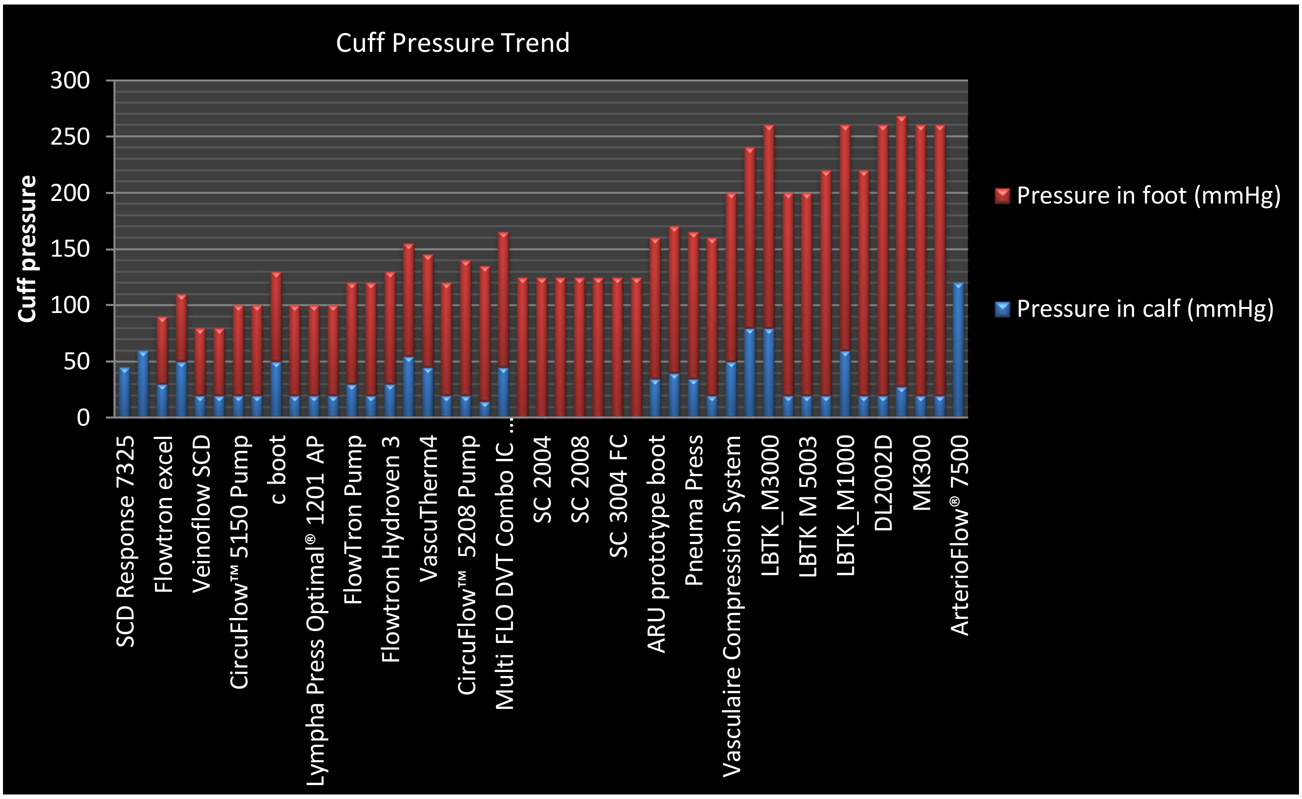


Fig 2.15: Cuff pressures variability of commercially available IPC devices. On the left side of the chart are the low cuff pressure devices (treatment of venous hypertension and DVT prophylaxis) and on the right the high-pressure devices (lymphoedema and arterial disease)

2.14.4 Single compartment sleeve devices

Mono- or single sleeve devices provide an attractively simplistic solution with just one sleeve, typically applied around the calf and using an expectedly uniform compression pressure. The problem arises at the proximal (just below the knee in the case of calf single sleeves) end of the sleeve. It has been shown that an occlusive "throat" which is a circumferential tight area of vessel collapse is formed when a vein is uniformly compressed externally. This happens because veins have high distal impedance, which makes their proximal part collapse first (Kamm 1986).

2.14.5 Dual and multi compartment sleeve devices

Multiple sleeve devices use sequential and usually graded pressures in a gradual manner with higher pressures in the distal sleeves. The device activates the cuffs inflation from the most distal (close to the foot) to most proximal. Once the target pressure is achieved, that sleeve remains inflated and inflation of the next one begins. Target pressures of the proximal sleeves are typically lower reaching to the lowest of all in the most proximal (closest to torso) one. This sequential action aims to “milk” the venous blood from the foot or the lower calf (depending on where the distal sleeve is applied) to the upper leg (Delis 2000).

2.14.6 Foot-calf-thigh IPC

Proctor (2001) showed that although many physicians believe full-length sleeves compress a greater volume of tissue and therefore provide a higher level of protection for patients at higher risk their team's data did not support this belief. In their work comparing calf and thigh long IPC sleeves the incidence of DVT was similar (3.4% vs 3.6%) among patients of similar age and risk of thromboembolism.

2.15 Compression modes

2.15.1 Sequential

By far, the most popular mode of dynamic compression, it necessitates the use of dual or multi-compartment sleeves. The compartments are inflated in a pre-determined sequence, typically from the periphery to the proximal leg. The rationale behind this mode of compression is to mimic the function of the foot, calf and thigh musculoskeletal pumps and “milk” the venous blood and the subcutaneous and skin fluid that causes leg oedema centrally.

This has the dual effect of treating venous hypertension and improving the skin’s microcirculation by reducing the leg oedema.

At the end of the compression cycle, the cuffs deflate allowing the blood to fill the veins again.

2.15.2 Graded

Graded or graduated compression refers to the difference in target pressures of the sleeve compartments. For this form of compression, at least two sleeves are required. It is commonly combined with the sequential mode. The pattern of the pressures grading follows their order of inflation. The most distal compartment is inflated to the highest of the range of pressures, followed by the next proximal which is inflated to a lower target pressure. Although there is no clear evidence, the reason of using this kind of grading is that the more distally a lower limb vein lies, the higher the intravenous pressure and the higher the pressure required counteracting to it.

Griffin (2007) compared three intermittent pneumatic compression systems in patients with varicose veins and showed that circumferential sequential graded compression was superior - in terms of volume expelled per hour – to uniform single chamber compression.

Kakkos (2005) compared a sequential, graded, three-chambered IPC device with a rapid inflation, two-chambered one and found the former haemodynamically superior when accounted for volume expelled per compression cycle and refill time.

Mosti (2012) argued that multi-component negative graduated compression bandages with calf compression pressure higher than ankle compression achieved increased venous calf pump ejection fraction compared to the traditional graduated compression bandage model.

2.15.3 Optimal compression pressures

Theoretically, any level of pressure below the leg’s arterial pressure can be used. The obvious reason is that the device should not function as a tourniquet interfering or stopping the blood supply to the lower leg.

2.15.4 Optimal “rest-to-best” or inflation time from baseline to set pressure

Another parameter, frequently ignored in IPC research, is the time that the device takes to achieve target compression pressures in the pneumatic cuffs. While some devices particularly the ones that operate using reservoirs - are fast to achieve the nominated target pressure; the majority does not mention this parameter in their operating manuals.

However, although devices that achieve target pressures fast also claim a high percentage of increment of the peak systolic velocity in the target vessel. Proctor (2001) found that devices that achieved the greatest per cent increase in peak systolic velocity also had the highest incidence of DVT. They concluded that this is a clinically untested finding that requires further investigation and they suggested a potential risk of increasing DVT from excessive tissue compression.

Kamm (1986) suggested that the delay time of the proximal applied compression should be longer than the cuff inflation rate and used short, 1 second duration cuff inflation rates. Delis (2000) used similar – short (0.5 – 0.6 seconds) - inflation rates while investigating optimal intermittent pneumatic compression stimuli for lower limb venous emptying.

Olson (1982) experimented on model leg with an intermittent graded pneumatic compression system using similarly short pressure rise times of 1 second.

Although fast inflation rates can be easily achieved by heavy IPC devices with large pumps, this would be challenging for a mobile, wearable device such as the one used in this dissertation.

2.15.5 Optimal compression cycle length

Compression cycle is defined as the time interval from the onset of inflation of the first sleeve to the next inflation of the same sleeve. This time includes the inflation and deflation of the sleeves and the resting period that follows to allow the veins to refill.

The cycle length can vary depending on:

1. The speed of inflation – directly proportional to the effectiveness of the pumping mechanism and valves used, as well as, the program's settings.

2. The duration of compression applied

3. The time that takes the sleeves to deflate – dependent on the valves and tubing used

One can see that, based on the above, compression cycles can theoretically last anytime from seconds to a few minutes and indeed they do in different types of devices.

Defining the optimal or best compression cycle length necessitates a definition of what optimal flow is in the case of lower limbs' venous return. That, in turn, depends on which condition the device is used for; treatment of venous ulcers, prevention of DVT, treatment of lymphoedema, treatment of arterial disease or sports recovery. An initial and logical approach would be to define the status of "normal" or "healthy" (venous, arterial, lymph vessel or muscular) function and try to emulate that status using the device. In other words, to restore the haemodynamic functionality in the case of venous ulcers and DVT prophylaxis, that is the main scope of this research.

2.15.6 Background of Existing Devices and Past Studies

The initial prototype IPC boot design was based mainly on knowledge gained through studying the existing literature. The most important early decision, which also played a crucial role in the choice of the exoskeleton, was to use three separate cuffs, instead of any other numbers.

A foot cuff was considered important, based on existing literature. Gardner and Fox (1983) described the foot venous pumping mechanism as consisting of an extensive network of veins located in the sole of the foot. Pressure application in the area, for example, during standing, activates this pump and the flow enhancement can be traced as far higher as the level of the femoral vein in the groin. Broderick et al. (2008) confirmed these findings and explained that longitudinal stretching of the foot plantar veins has a significant impact on blood flow.

Kamm (1982) compared three different compression modes: uniform compression (the application of uniform single pressure compression along a single sleeve), graded compression (simultaneous compression of non-uniform pressure starting from a maximum at the level of the ankle and falling to a minimum proximally) and wavelike compression (progressive application of uniform pressure that starts at the ankle and proceeds higher in a wave-like fashion). They concluded that the wavelike mode is more effective in producing the near-complete collapse of all veins. In addition, they noted that graded and wavelike compression provided increased and more uniform velocities and increased shear augmentation compared to uniform compression. Furthermore, Kamm and Shapiro (1979) showed that uniform (same compression pressure applied in a single cuff) compression can cause an occlusive “throat” in the proximal segment of a vein undergoing compression, thus trapping blood in the vein instead of propelling it.

Janssen (1993) compared the enhancement of venous blood flow triggered by two devices: one with a single cuff applying uniform compression and one with three cuffs, applying sequential, graded compression. Their findings suggested that the sequential graded compression device maintained a higher average blood flow rate and propelled a greater volume of blood with each compression cycle compared to the single sleeve uniform pressure device.

Nikolovska (2005) focused on the improvement of clinical outcomes (venous ulcer healing) and compared a two-cuff (calf and thigh) rapid inflation device (0.5 seconds to target pressure) and 6 seconds duration of inflation followed by 12 seconds of deflation with a slow inflation (60 seconds to target pressure), compression for 30 seconds and deflation for 90 seconds. The pressures used were 50 mmHg for the calf and 40 mmHg for the thigh. The rapid inflation device achieved ulcer healing rates of 86% whereas the slow inflation one achieved 61%.

Morris (2006) compared the fibrinolytic effects (TFPI and plasminogen activator activity) of rapid and slow IPC devices and found no differences.

Kamm and Butcher (1986), performed radionuclide studies on healthy volunteers to compare different modes of compression including uniform, graded, sequential, combined graded and sequential compression, using a three-cuff device. They concluded that a combination of sequential and graded compression resulted in optimal haemodynamic results.

Nikolaides and Fernandes (1980), used radionuclide and ultrasound studies to compare the efficacy to prevent Deep Venous Thrombosis (DVT) of an intermittent, sequential, graded, pneumatic compression device with a uniform, single sleeve device and administration of anticoagulant (low molecular weight heparin). Their results showed that the sequential multi-sleeve device was as effective as heparin and more effective than the single-sleeve device.

2.16 Gap in knowledge

Although IPC is an ever-growing popular medical technology, there is little information, knowledge or significant literature concerning the optimum settings that should be used. Another relevant question is whether IPC should be patient-specific. Only one device uses a feedback mechanism but there is no research linking improved function. The feedback only changes the frequency of its function but not the pressures or the time length of compression. The device used in this study has a feedback mechanism is fully adjustable and hence unique.

2.17 Aim of the study

The aim of the present study is to explore the uncharted territory of intermittent pneumatic compression with a view to defining the ideal parameters in terms of pressures, timings, number and position of cuffs and length of treatment. The important questions that this study will attempt to answer are i) the optimum pressure to maximise venous return, ii) the optimum deflation time that will maximise venous return and iii) whether IPC should be personalised to patients.

Chapter 3 - Methods

3.1 Introduction

There is a need to fill the gap in knowledge surrounding the effect of intermittent pneumatic compression (IPC) on the behaviour of lower limb venous flow. A number of different methods to investigate blood flow are covered in the literature, including invasive phlebography and plethysmography, duplex ultrasonography and air plethysmography; all of them have advantages and disadvantages.

The primary goals of this study were to; (1) design and develop an IPC prototype and (2) investigate the sensitivity of the healthy cohort's haemodynamics to changes in cuff pressure magnitudes and duration parameters. The independent variables are compression pressure values and durations; the measurable outcome is stroke distance (velocity-time integral) to assess venous flow changes.

3.2 Research Design

The study consists of two phases: the design and development phase and the testing phase. The initial prototype IPC boot was designed, following an extensive literature search and based on previous findings, as well as clinical experience (the doctoral candidate is a vascular disease surgeon).

The initial phase consisted of the design and development phase of a produced prototype IPC boot with an integrated control system for data collection of the independent (compression pressure and duration) and dependent (stroke distance) variables. This involved an iterative process, consisting of continual improvement on the prototype IPC boot design until repeatable data could be collected. The prototype was then used to suggest a range of variable values (compression pressure and duration) to investigate the second phase of the study.

The testing phase of the project incorporated a pilot study (n=40 healthy subjects) to test the aforementioned hypotheses. Objective haemodynamic data and statistical analyses were collected to test each hypothesis. The relationship between compression pressure, duration values, and stroke distance was investigated to understand the effect of the IPC on the haemodynamics of the popliteal vein and to optimise the performance of the IPC boot.

The prototype IPC boot evolved through three different versions:

I. The version I consisted of an all-mechanical prototype, with a spring pump under the foot that was driven by the walking movement to inflate the cuffs.
II. Version II replaced the spring pump was replaced by a control system and external pump to provide compression in the cuffs while the foot was not moving.
III. Version III was simplified to optimise the system by eliminating components that did not contribute to improving the haemodynamics effect in the popliteal vein, as identified in the preliminary testing. This was, therefore, a faster and more user-friendly prototype than version II. The final tests were performed, using this latest version.

The commercially-available IPC devices do not have mechanisms that would allow full control of their functions and were therefore not suitable for this project.

3.3 Design criteria of the Prototype IPC Boot

The prototype IPC boot in this study was designed to mimic the physiological muscle calf and foot pumps (the muscles), as described in the literature, applying external sequential pressure to the lower limb in the form of pneumatic compression. The prototype IPC boot was designed such that (i) the testing parameters (compression pressure and deflation time) could be easily changed and (ii) the corresponding outcome measures (haemodynamics effects) could be measured in real time to test the hypotheses.

The technical features considered for the prototype IPC boot design include:

I. Number of cuffs (one, two three, multi-chambered)
II. Anatomical areas compressed (foot, lower calf, upper calf, thigh or a combination)
III. Extent of anatomical area covered (circumferential or asymmetric)

The functional parameters include:

I. Compression mode (sequential or uniform)
II. Compression grading (different cuff pressures or not)
III. Compression frequency (number of compression cycles per minute)
IV. Length of compression cycle
V. Length of deflation period
VI. Magnitude of cuff pressure (cuff target pressure)
VII. Length of time of individual cuff compression
VIII. Time required to achieve target cuff pressure (how fast the cuffs are inflated)
IX. Use of baseline (background) compression

Figure 3.1: Compression device: Technical features (1+2). In this case, there are three cuffs covering the anatomic areas of foot, ankle and calf cuff.

3.4 Design and Construction of the Prototype IPC Boot

The initial prototype design was based on relevant information from the literature. The number of cuffs and initial setting limits for the pressure and duration parameters, used to design and test the prototype, were based on a combination of settings used by relevant commercial devices. The design criteria included the following:

I. The prototype should be designed with completely adjustable pumping and timing parameters.

II. A central controlling mechanism that can be connected to different sizes of prototypes.

III. The configuration of the exoskeleton-cuffs should allow the use of a Doppler sensor to be placed over the popliteal vein behind the knee.

IV. The device could be used for future research with a multitude combinations of settings and body positions, not only in healthy subjects but also on patients with venous disease in future studies, making it a valuable tool for further understanding of venous haemodynamics.

The prototype device was designed to bear three cuffs, supported by an exoskeleton, covering the foot and the entire calf to knee level (Figure 3.1). The cuff-exoskeleton combination was powered by an electronic pump. All prototype functions were controlled by a microprocessor, electronic valves, and pressure sensors. An intuitive bespoke software programme controlled the microprocessor. A schematic depiction and description of the prototype are shown in Figure 3.2.

Figure 3.1: Intermittent pneumatic compression boot, showing non-circumferential (asymmetric) cuffs. The cuffs do not cover the front (arrow) of the boot internally, area corresponding to the tibia (anteromedial calf)

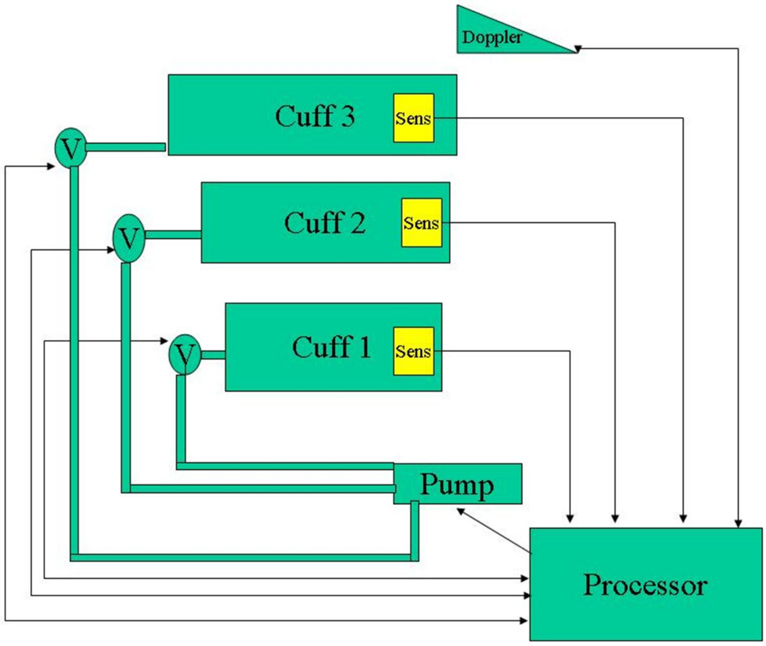


Figure 3.2: Schematic diagram of the prototype hardware.
V= Electronic computer programmable three-way valves.
Sens = Pressure sensors fixed inside the cuffs, used only for reliability tests
Cuff 1 = Foot cuff. Cuff 2 = Ankle cuff. Cuff 3 = Calf cuff

The functional parameters of the IPC boot used in this study are illustrated in Figure 3.3. These parameters include baseline compression, cuff pressure levels, cuff pressure grading, duration of the compression cycle, deflation time and frequency of compression to target cuff pressure, the sequence of cuff compression and duration of compression of individual cuffs.

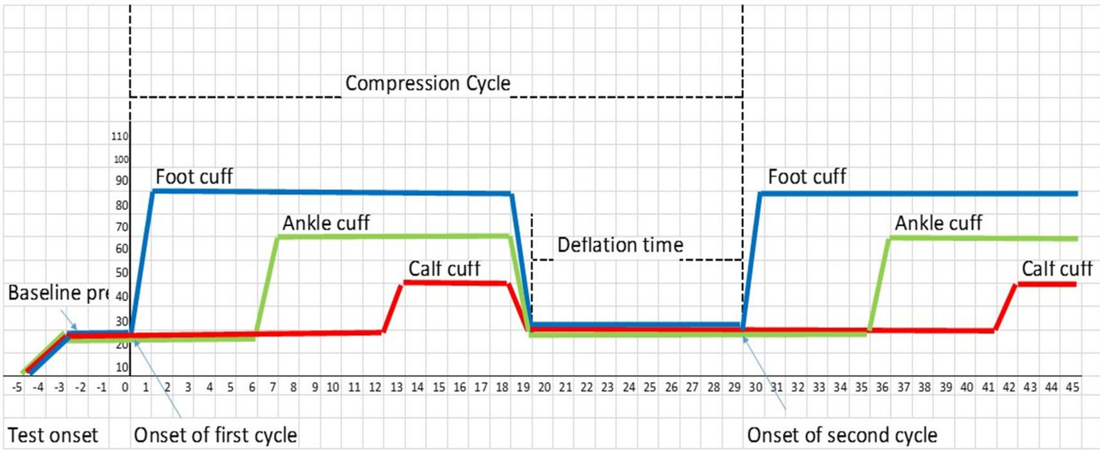


Figure 3.3: Depiction of the functional parameters of a Pneumatic Compression (PC) device showing the baseline compression, cuff pressure levels, cuff pressure grading, duration of compression cycle, deflation time and frequency of compression

3.5 Components of the IPC boot prototype

3.5.1 The Cuffs

In addition to the foot cuff, a cuff placed just around the calf (the calf cuff) was considered essential as the upper calf contains the largest parts of the major calf veins, including the peroneal and tibial veins. A third cuff (ankle cuff) placed between the foot and calf cuffs, around the ankle. Using a larger number of cuffs would have made the device more complex and increased the power demands (Figure 3.4) on the pump.

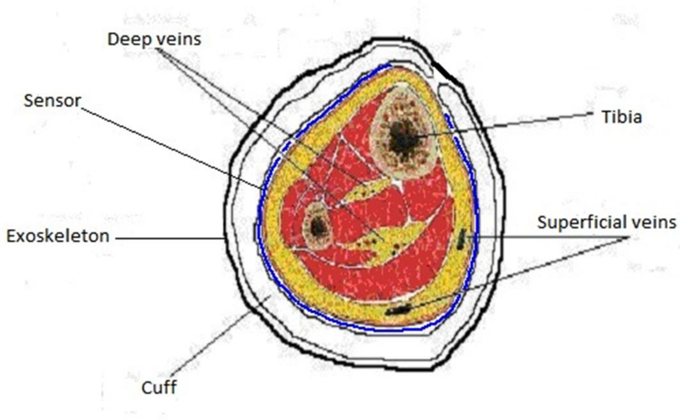


Figure 3.4: Exoskeleton, cuffs, sensors positioning and lower limb at the level of the mid-calf in the transverse plane. (Adapted from Gray's Anatomy)

All three cuffs were horizontally secured in a zipped boot, made from neoprene, in such a way that, when the boot was worn with the zip fastened, the cuffs would cover the internal (inside) perimeter of the respective levels of the foot, ankle or calf with the exception of the area over the tibia, where there was less soft tissue (Figure 3.1). The presence of a zip was considered important; without it, the process of wearing and taking off the device would have been laborious and the frequent use would eventually damage the cuffs. The cuffs were secured to the exoskeleton with through and through durable threads in places that would not get in contact with the participant's skin.

The cuffs were manufactured from commercially-available blood pressure measurement aneroid sphygmomanometers of different sizes to accommodate the surface of the anatomic area they were meant to cover. Each cuff consisted of a latex one-piece homogeneous bladder enveloped in a sheath of soft, skin-friendly fabric. Two tubes in each cuff provided two entry (or exit) points, one was used to inflate and deflate the cuff and the other was used to verify the cuff pressure when connected to a mechanical manometer.

The three internal cuffs (Figure 3.5) were chosen as follows: (i.) Proximal calf: 1869-DC-FF - Large arm Calibrated V-Lok cuff and bag with 2 female Colder/Locking Connectors, (ii) Distal calf:1880-DC-FF - Adult Calibrated V-Lok cuff and bag with 2 female Colder/Locking Connectors and (iii) Foot 1881-DC-FF - Child/small adult Calibrated V-Lok cuff and bag with 2 female Colder/Locking Connectors.

Figure 3.5: The internal cuffs fixated inside the exoskeleton

Each cuff as shown in Fig 3.6 consists of a latex one-piece homogeneous bladder enveloped in a sheath of soft skin-friendly fabric. The two tubes in each cuff provide two entry or exit points, one used to inflate and deflate the cuff. During reliability testing one of the orifices was connected to an analogue manometer which provided real-time data.

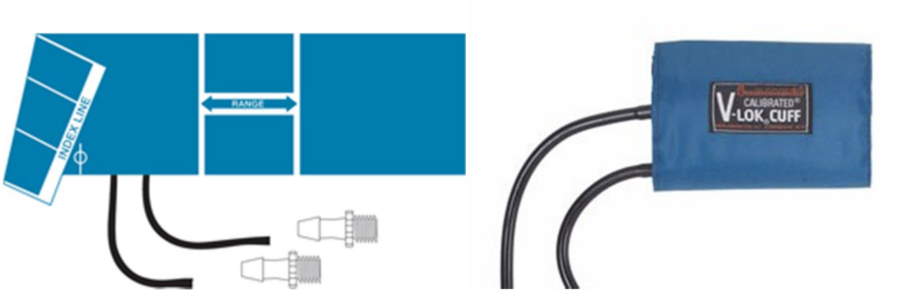


Figure 3.6: The cuffs with their tubing

3.5.2 The Exoskeleton

An exoskeleton was included in the prototype IPC boot design as the cuffs alone needed an increased amount of air, and hence time and pump energy, to achieve reasonable levels of pressure. Additionally, the exoskeleton offers a fixed position for the cuffs so they do not have to be repositioned during testing, thereby reducing the risk of excessive variability. The material chosen for the exoskeleton was small strain rubber to allow a minor degree of expansion to accommodate different leg sizes.

The exoskeleton is essentially a knee-level boot (Hunter's Balmoral Neoprene Zip model) with a zip on the lateral (outer side), which functions, both, as a safety measure (for example, to release the leg in case of device failure) and to allow the easy wearing of the boot. The original first prototype size was a UK size 11, chosen to fit a normal UK size 10 foot, in addition to the bladder assembly. That allowed enough space for the foot cuff to be placed internally across the middle part of the foot down to the origin of the toes (Figure 3.7).

Figure 3.7: The exoskeleton and schematic representation of the position of the cuffs

3.5.3 The Tubes

Five-mm outer diameter silicon elastic tubes (Figure 3.8) were used for all the connections between the pump, valves, pressure sensors and cuffs. Five-mm inner diameter plastic T-connectors were used to connect the tubes, as necessary.

Figure 3.8: Five-mm outer diameter silicon tubing to connect the components

The total length of tubes was kept as short as possible in order to avoid dead space and delays in inflation and deflation. Inevitably, however, the tubes used in the control system could be partially responsible for any occasional prolonging of the inflation/deflation times.

3.5.4 The Pump

The pump (Scoocom, Quandong, China) used in the prototype is a diaphragmatic microelectronic air pump (Figure 3.9) with key specifications shown in Table 3.1.

Table 3.1: Key specifications of the pump

Parameters	Values
Rated voltage	DC 6.0 V, DC 12.0 V, DC 24.0 V
Rated current	<430 mA, <300 mA, <150 mA
Leakage	<3 mmHg/min from 300 mmHg in a 500 cc tank
Air flow rate	>1.8 l/min
Max pressure	>500 mmHg
Inflation time	<10 s from 0 to 300 mmHg in a500 cc tank
Environment	0-50 ° C, 75RH

Figure 3.9: Miniature electronic air pump

3.5.5 The Valves

Miniature solenoid miniature valves (Sensortechnics, MA, USA)) (Figure 3.10) were selected, given their small size (8 mm wide), versatility and, most importantly, because they are electronically computer programmable. Each 3-way switching solenoid valves had three possible states to regulate the volume of air in the cuffs: normally closed

(NC), normally open (to air) (NO) or distributor (to tubing system). Appropriate size tubing was connected directly to the valve ports. They were installed on a manifold and connected through wiring to a Printed Circuit Board (PCB) board where a Programmable Intelligent Computer (PIC) microcontroller is mounted. The key specifications of the solenoid valves are shown in Table 3.2.

Table 3.2: Key specifications of the solenoid valves

Physical Properties	Weight: 4.5 g (0.16 oz)
Operating environment: 0...50 °C	Internal volume: 0.074 cm^3 (0.0045 in^3)
Storage temperature: -40...70 °C	**Media Compatibility**
Length: 24 mm (0.92 in)	Non-reactive gases and selected liquids
Width: 7.9 mm (0.31 in)	
Height: 9.5 mm (0.375 in)	**Electrical Power**
Spacing: 8 mm (centerline)	TX3P006:... (6 psi) 0.5 W
Porting Universal barbs for 1/16 in I.D. tubing	all others :(30 psi, 100 psi) 1.0 W
(1/32 in wall max.) or	Voltage: 3, 5, 12, 24 VDC
manifold mount with gasket	Electrical connections: PC pins, 4 mm centers
	Wetted Materials:

PBT (polybutylene terephthalate); 430 series stainless steel; 302 series stainless steel (passivated); FKM (fluoroelastomer); EPDM (ethylene propylene diene monomer); silicone

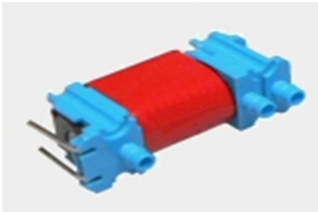


Figure 3.10: Computer programmable 3-way valve used to regulate the volume of air in the cuffs

3.5.6 The Pressure Sensors

Five electronic Smartec SPD015GA pressure sensors (Smartec, Breda, Netherlands) (Figure 3.11) were used to monitor the air pressure in the system, feedback to the microcontroller, which, in turn, regulates the valves function, allowing them to operate accordingly. The key specifications are shown in Table 3.3.

Table 3.3: Key Specifications of the pressure sensors:

Parameters	**Values**
Performance Characteristic at Vcc	5 V excitation at 25 °C
Supply Voltage	2.7, 5, 5.5 V
Supply Current	2.5 mA
Pressure range (fs)	15 psi
Zero Output	0.481, 0.5, 0.519 Vdc
Span Output	3.981, 4.00,

	4.019 Vdc
Max output current	2.2 mA
Accuracy	±0.5 %FS
Response time	25 ms
Pressure overload	3x psi
Operating temperature	-20 - 85 °C

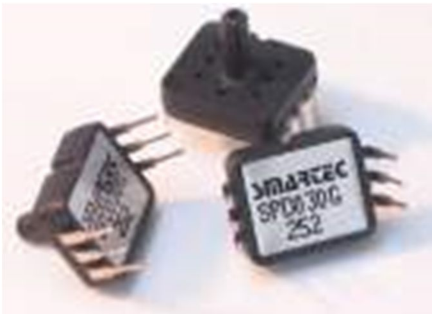


Figure 3.11: Pressure sensors used to monitor pressure in the system

3.5.7 Programmable Intelligent Computer (PIC) Microcontroller

A 14-pin microcontroller Atmel, San Jose, California (Figure 3.12) is programmed to regulate the function of the components and to oversee the smooth operation of the device. The key features of the microcontroller are listed below:

Compatible with MCS®51 Products

• 20 MIPS throughput at 20 MHz clock frequency and 2.4 V, 85°C operating conditions

• Single clock cycle per byte tech

• 2/4 kilobytes of In-System Programmable (ISP) Flash memory

– Serial interface for program downloading

– 32-byte fast page programming mode

– 32-byte user signature array

• 2.4 V to 5.5 V VCC operating range

• Fully static operation: 0 Hz to 20 MHz

• 2-level program memory lock

• 256 x 8 internal RAM

• Hardware Multiplier

• 15 programmable I/O Lines

• Configurable I/O with quasi-bidirectional, input, push-pull output, and open-drain modes

• Enhanced UART with automatic address recognition and framing error detection

• Enhanced SPI with double-buffered send/receive

• Programmable watchdog timer with software reset

• 4-level interrupt priority

• Analog comparator with selectable interrupt and debouncing

• Two 16-bit enhanced timer/counters with 8-bit PWM

• Brown-out detector and power-off flag

• Internal power-on reset

• Low power idle and power-down modes
• Interrupt recovery from power-down mode

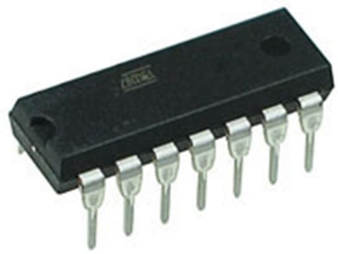


Figure 3.12: The microcontroller that regulates the function of the components.

3.5.8 The Doppler device

The efficacy of applied intermittent pneumatic compression can be assessed, by measuring the change in blood flow occurring in the popliteal and/or femoral vein. Lyons (2002) and Clark-Moloney (2006) chose ultrasound assessment of the peak velocities in the popliteal vein during electrical neuromuscular stimulation to evaluate the augmentation of venous flow caused by the calf muscle contraction. Doppler ultrasonography is a safe and non-invasive method of evaluating blood circulation within vessels in real time. The method was based on the transmission and reflection of ultrasound. A widely accepted method of choice for haemodynamic assessment of blood flow is colour Doppler ultrasonography.

To assess the efficacy of the applied compression in this study, the changes of blood velocity were traced in the popliteal vein at the level of the popliteal fossa (the area behind the knee joint). In this anatomic area, the popliteal vein follows a superficial and, thus, relatively easily detectable course of approximately 2cm under the skin. The popliteal vein at this level is the main venous blood draining vessel.

An RD2 Continuous Wave Doppler system (Huntleigh, Cardiff, UK) with an 8-MHz flat probe was used for this purpose (Figure 3.13). The piezoelectric crystals are mounted at a 45^{o} angle on the probe. Securing the flat Doppler probe to the area of the popliteal fossa was a challenging process. The difficulty came from the following facts:

I. The popliteal fossa is an anatomic area where the skin folds, especially when the knee is flexed or when the subject is walking.
II. All probes require a small amount of conductive gel material (coupling gel) to operate. This makes securing the position with sticking pads or similar materials very difficult as the probe with the pad tends to slip and lose accurate positioning which is crucial in receiving a strong signal from the underlying vein.
III. Achieving a strong venous flow signal also requires (1) a degree of pressure between the probe and the skin so there is perfect contact and (2) the probe-vein distance is the minimum possible.

The above problem was solved by using a wide Velcro bearing elastic band around the knee that fixed the probe in place on the skin overlying the popliteal vein (Figure 3.13). The flat probe was attached firmly in the centre of a 45-mm suction cup with the help of a 10-mm circular double sided adhesive pad.

Figure 3.13: The Doppler device and the elastic band with the miniature flat probe to trace blood flow in the popliteal vein

The concave side of the suction cup hosting the probe was filled with a conventional ultrasound transmission gel material that functions as a contact medium between the probe and the participant's skin. During the first testing sessions, however, it became obvious that this material, due to its low viscosity, was making the system cup-probe suction highly unstable and, hence, prone to a high rate of interference, especially when the subject moved. The natural gliding properties of this material, usually welcomed for a clinical ultrasound and Doppler use, were, in this case, proving unnecessary and detrimental for the purpose of this project.

Ultrasonic media are water-based gels whose main purpose is to transmit the acoustic energy from the probe to the tissues with the minimum possible loss while traveling through these structures. This is avoided by minimising the phenomena of reflection and refraction. Traditionally, gels used for this purpose are water based with a high degree of gliding to allow fast and frictionless scanning when using the probe in a large area that requires views from different angles and locations. The needs of the current research were different and the low viscosity of the existing ultrasound gel was causing difficulties in maintaining the probe at the desired position and caused interferences. Attempts were made to use similar, but more viscous material.

The substance that fulfilled all the criteria of high sound wave conductance, good contact with the probe and the skin with no air gaps, skin-friendly profile and high viscosity, was the material currently used to manufacture the popular children toy, known as "slime". Its main components are guar gum (a polysaccharide) and sodium tetraborate. As alternatives to the polysaccharide, other (alcohol-based) polymers have been used to create the same result. This substance was used comparatively to the traditional ultrasound gel in the lab and gave identical results in terms of data received during Doppler scanning. In addition, it did prove to have solved the problem of interference and probe/cup position shifting. As a bonus, it did not leave any visible remnants behind after the removal of the probe, leaving the skin clean and dry as opposed to the ultrasonic gel that always requires wiping off (Figure 3.14).

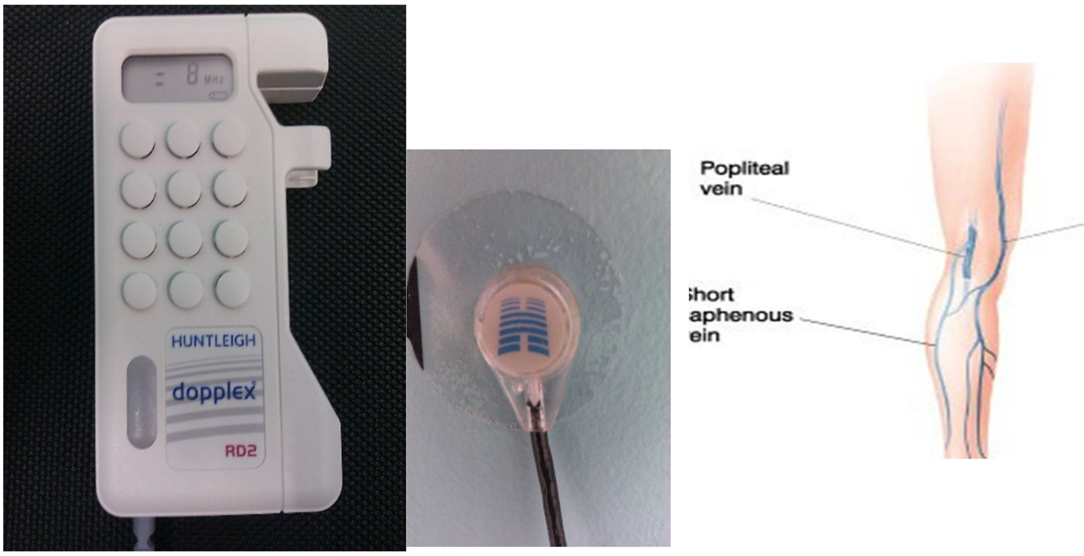


Figure 3.14: Left: The Doppler signal acquisition system with an 8MHz probe and Right: the location of the popliteal vein in the popliteal fossa.

3.5.9 The control software

Two versions of controlling software have been used over the course of this research. The initial version will be discussed in the section called "Previous versions of the device" section. The current form is the one that was used for the final extensive testing on participants. This version is built and functions in the Android operating system (Figure 3.15-3.17).

Three-way electronic computer programmable valves were used in the following positions:

ON: Permits cuff inflation)

OFF: Blocks the tubing, maintaining pressure

DEC: Cuff decompression

The operating cycle has the following sequences:

I. The cycle starts with V1 ON, V2 OFF, V3 OFF.
II. The pump starts functioning with V1 ON, V2 OFF, V3 OFF
III. C1 inflation
IV. When PC1 becomes optimal, then S1 switches V1 off and V2 on
V. C2 inflation (while C1 still inflated)
VI. When PC2 reaches set pressure, S2 switches V2 off and V3 on
VII. C3 inflation while C1 and C2 still inflated
VIII. When PC3 becomes optimal, S3 switches V3 off and then switches all valves to DEC mode decompressing all cuffs
IX. After a "decompression" period of 20 seconds, determined by low, baseline (20mmHg) cuff pressures PC1, PC2, PC3. The valves go to start mode (V1 ON, V2 OFF, V3 OFF)
X. The pressure sensors provided the microcontroller with a continuous feedback of the final pressure applied to the limb. A maximum pressure set point protects the limb from inappropriately high levels of compression. The overall pressure to the limb was estimated to be the sum of the cuff pressure and the pressure imposed by the elastic material of the exoskeleton. This pressure is dynamic and changes according to the limbs shape, position, movements, and presence of dressings. Particularly, with respect to the limb's shape, many patients with chronic venous insufficiency have typical "champagne bottle" calves with thin lower legs/shins and disproportionately larger upper calves.
XI. The Doppler waveform obtained provided feedback for the efficacy of the compression during every cycle. The Doppler probe traced normal blood flow in the veins during the compression cycle towards the torso. It was also an important index tool to ensure the system achieved the minimum effective compression. In this way, the compression did not have to be unnecessarily

too high/uncomfortable. In addition, the energy consumption of the prototype can be limited to the minimum.

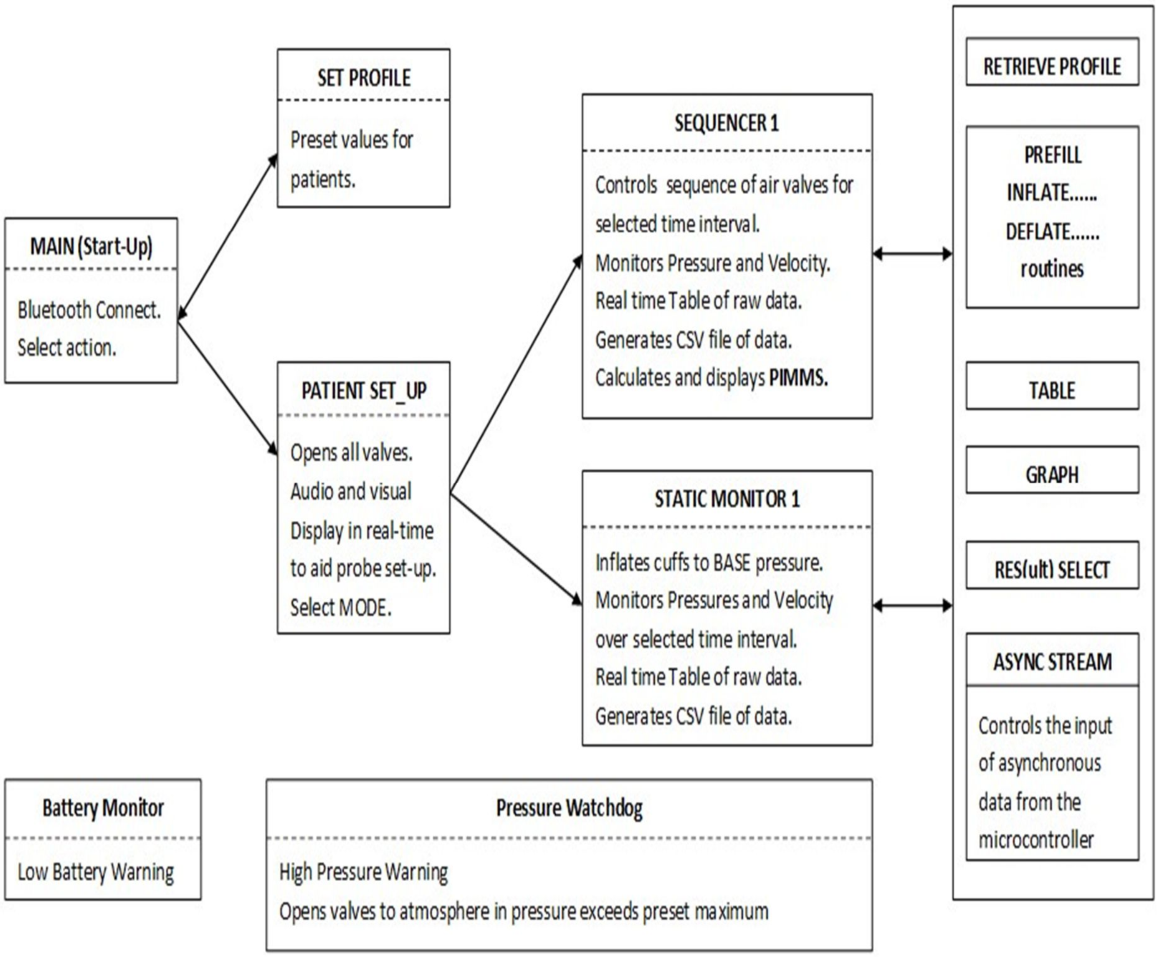


Figure 3.15: Roadmap of control software in an Android environment

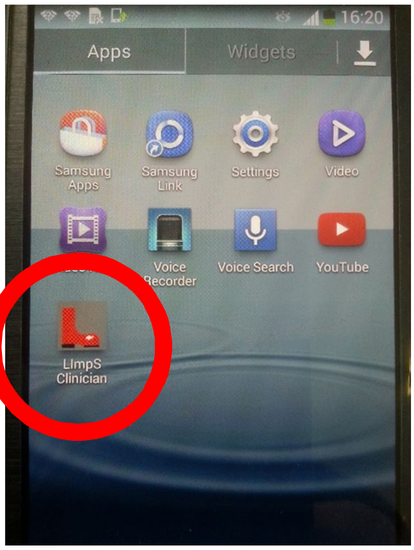


Figure 3.16: The control/data collection/feedback features of the application software (App)

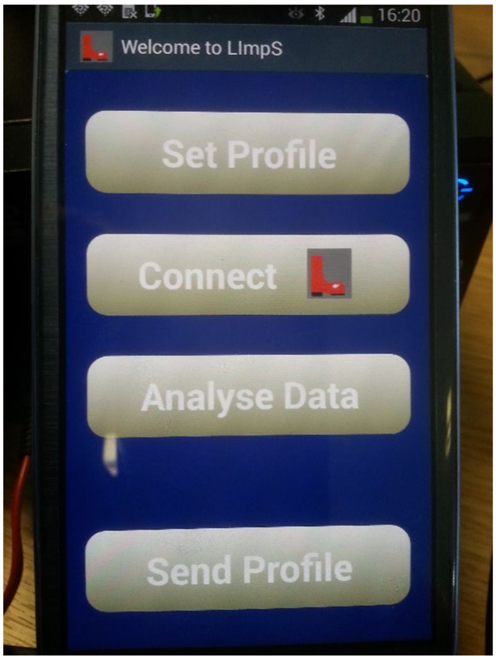


Figure 3.17: The opening page with different options in the older software version

The control software allows the user to option to perform functions, including:

I. setting the compression profile, including target pressures, the length of cycles, timings;
II. Bluetooth wireless connection to the control box which contains the pump, valves, and microcontroller
III. data analysis, including recently collected data, and data collected by an older version of the device;
IV. a send profile option for an eventual patient-operated version of the software.

3.5.10 Visualisation on Smartphone

A Samsung S3 mobile smartphone with an Android 4.3 operating system was used to operate the controlling software and data collection system (Figure 3.1.8). Version II of the device used an interface program running on windows operating system environment. The software was modified for use on a mobile unit and different operating systems for the following reasons:

I. Adopting a mobile device, such as a smartphone, takes the IPC device a step closer to full autonomy, true mobility and freedom of movements
II. Its Bluetooth wireless capacity eliminates one more of the hard wire connections making the device lighter and more mobile
III. The widespread use of mobile devices and their applications have popularised and made more people familiar with their use. Data collection and software control comes in two versions: a clinician and a patient one.

Figure 3.16: The Samsung Galaxy SIII smartphone is used to run the data collection and device control

3.6 Evolution of the Prototype IPC Boot Design

The prototype IPC boot has evolved through different forms and stages of testing to solve problems that were encountered during testing and to improve its performance and design.

3.6.1 Version I of Prototype IPC Boot Design

The original version of the prototype IPC boot was designed to be self-powered; it had a purpose-made bellows pump and spring mechanism incorporated in the sole of the boot, operated mechanically with every footstep, instead of an electrically-operated pump. Each step would force air from the bellows pump through appropriate tubing, inflate the cuffs. This first prototype version also had an air reservoir to store excess air that could be used to fill the cuffs during periods of immobility.

The control system was very similar to the one in the final design, including the control valve, pressure sensors, and microprocessor. The initial prototype IPC boot was completely tethered to the control system and the computer; the blue tooth system was not installed in the first prototype version. This earlier version did not have a Doppler sensor to measure changes in blood flow. This was because the aim was to identify any major issues with the prototype design for continual improvement, not to assess its performance.

3.6.2 Evaluation of the Design of Prototype IPC Boot, Version 1

Two prototypes of this kind were constructed and tested on one healthy subject in a gait lab to find out whether any of the incorporated components (spring and bellow pump mechanism, cuffs, and control system) affected the subject's gait. Kinetics and kinematics and plantar pressure data were collected, using (i) Kistler force plates (Kistler Group, Hampshire, UK), (ii) a Vicon optical motion tracking system (120Hz) (Vicon, Oxford, UK) with 9 synchronised cameras and (iii) a Pedar plantar pressure measuring system (Novel, Munich).

The testing protocol included walking (i) barefoot, (ii) in a boot with no cuffs and no pump, (iii) in a boot with only a foot cuff, (iv) in a boot with a foot cuff and an ankle cuff, (v) in a boot with a foot cuff, an ankle cuff and a calf cuff and (vi) in a boot with three cuffs and a bellows pump fixed in the heel area of the sole. The same prototype footwear (right foot) was used for the different tests to reduce variations. The other (left) foot was shod with the left side of the same footwear, unmodified, in order not to induce any gait asymmetry during data collection.

The data, compiled in Table 3.4, show that the components in prototype IPC boot (cuffs, control system, bellows pump and spring mechanism) did not affect the kinematics (Table 3.4), ground reaction forces (Figure 3.17) and joint moments (Figure 3.18) between the different testing conditions. The pressure distribution data between the foot sole and the insole of the unmodified and prototype boots, however, showed a high increase in pressure values in the area corresponding to the spring and bellow pump mechanism. These results show that the cuffs and control mechanism could be safely used in the prototype an alternative location and design of the pump system was required.

Shoe type	Step length (m)	Walking velocity (m/s)	Stance time (s)
Bare foot	0.88 ± 0.01	1.5±0.0	0.7±0.0
Boot – no cuffs	0.84 ± 0.02	1.6±0.0	0.7±0.0
Boot with 1 cuff (foot)	0.83±0.01	1.6±0.0	0.6±0.2
Boot with 2 cuffs (foot and ankle)	0.83±0.002	1.6±0.0	0.7±0.0
Boot with 3 cuffs (foot, ankle and calf)	0.85±0.01	1.6±0.0	0.7±0.0
Boot wit 3 cuffs and Bellows pump (sole)	0.83 ± 0.01	1.6±0.0	0.7±0.0

Table 3.4: Temporospatial data when walking barefoot, wearing the unmodified boot, wearing the prototype IPC boot with different number of cuffs and with and without bellows

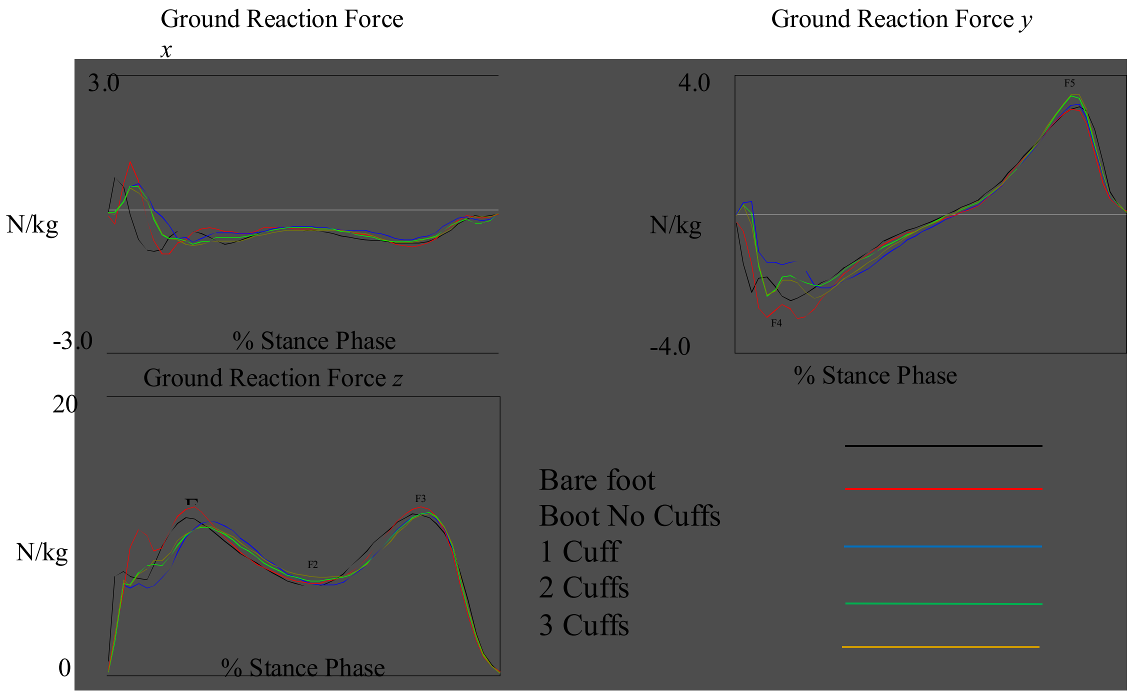


Figure 3.17: Ground reaction forces of participant walking barefoot, wearing the unmodified boot, wearing the boot with different number of cuffs and with and without a bellows pump.

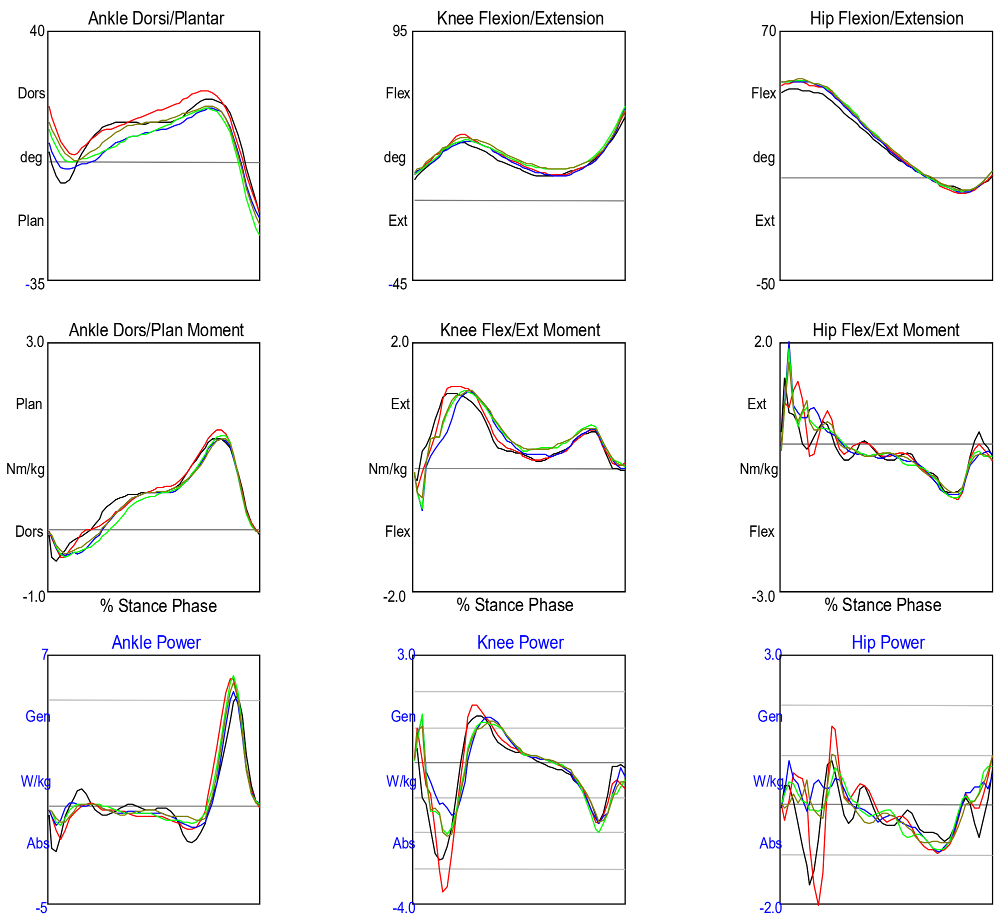


Figure 3.18: Joint moments of participant walking barefoot (black curve), wearing the unmodified boot (red curve), wearing the prototype IPC boot with different number of cuffs (blue, green, yellow curves) and with and without a bellows pump

During testing of the initial prototype IPC boot, it was observed that the compression could be maintained for a few minutes after walking, even with the addition of a reservoir to "store" air for a period of immobility. From a clinical point of view, individuals who need compression are the ones with poor mobility. Indeed, Clarke-Moloney (2007) showed that patients with venous ulcers take fewer steps per week compared to controls. Therefore the IPC boot needed to be functional even during long periods of immobility.

3.6.3 Version 2 of Prototype IPC Boot Design

Version 2 of the prototype IPC boot, an all-electronic approach was adopted to replace the bellows pump and spring mechanism in order to sustain long-term, effective compression, especially during periods of rest. Moreover, the bellows pump and spring mechanism, positioned in the boot insole, increased the plantar pressure in that area, which could lead to pressure ulcers and related health problems. For these reasons, the mechanical pump in the boot insole was replaced with an electronic pump.

However, the second prototype version would require a higher electrical energy consumption, due to the electronics pump, and, inevitably, a higher degree of complexity. Although the final prototype was supposed to be fully mobile, with rechargeable batteries, and wirelessly-controlled micro-components, the second version prototype IPC boot was powered by the mains supply. The reasons were due to the fact that the proof of concept had yet to be achieved and that the initial funds secured would not suffice for to develop a fully-mobile prototype version. Eventually, however, both these requirements were met successfully and the device evolved to its final version.

The second version of the IPC boot prototype is illustrated in Figures 3.19 and 3.20. The configuration of the exoskeleton and cuffs remained the same. In order to gain full control of the functional parameters, the system should allow reliable, fast, safe and user-friendly control of its functions. A system that was able to fulfill all these criteria was built, consisting of a PIC microcontroller, an electronic pump, programmable electronic valves, cuff pressure sensors and tubing connecting the pump to the cuffs. The microcontroller was programmed using Visual Basic-based bespoke software, running on Windows 2000 operating system. At the time it was considered important to have an extra cuff acting as a reservoir which was incorporated in the device.

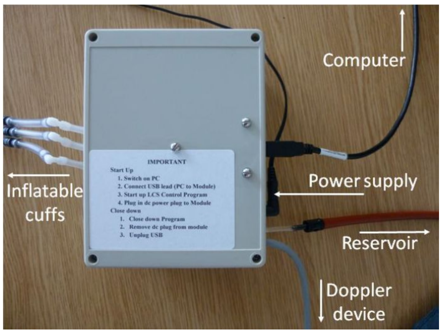


Figure 3.19: Control mechanism of prototype IPC boot, Version II

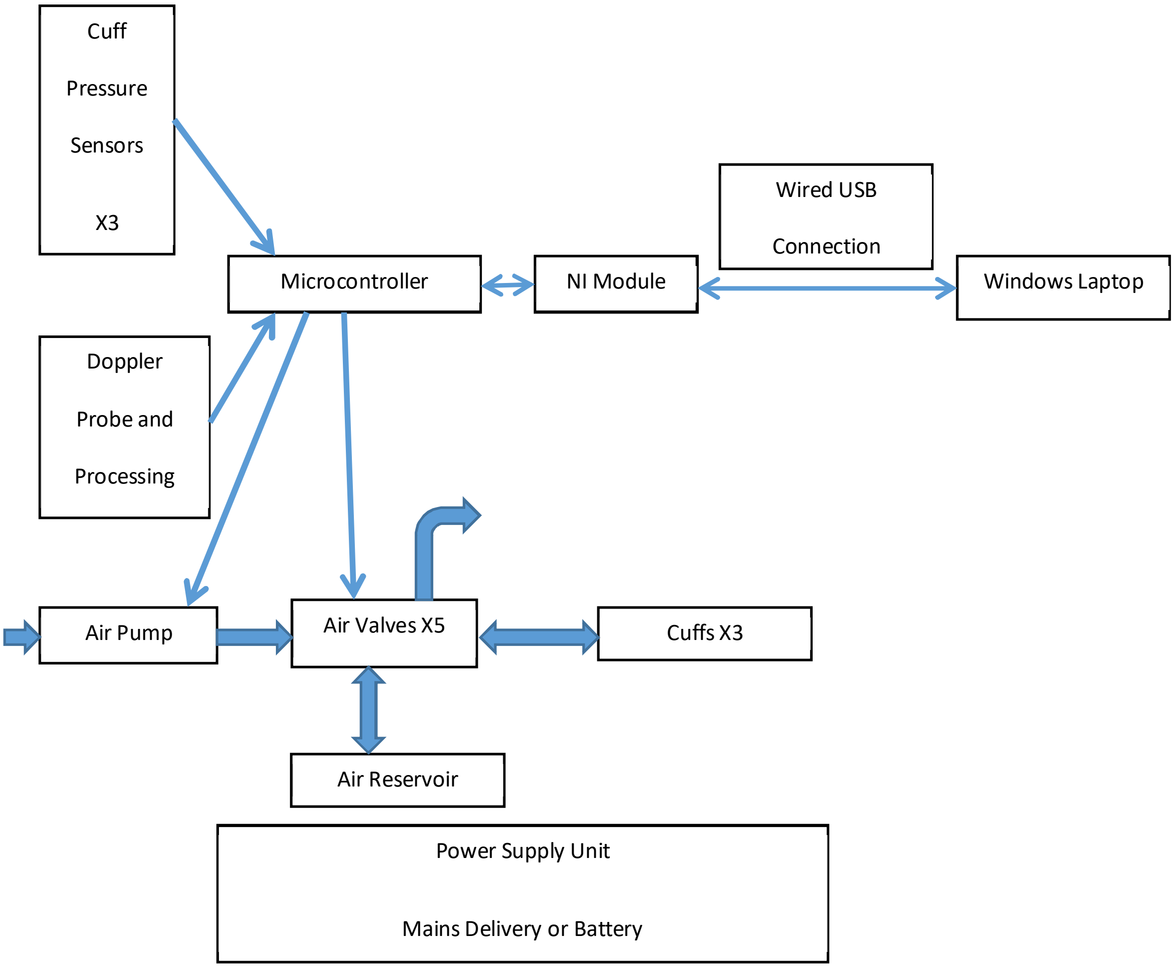


Figure 3.20: Operational flowchart of Prototype IPC Boot Version II Hardware. NI = National Instruments (Austin, Texas, US)

The initial version of the control software was created in Visual Basic software to allow control of all the functional parameters of the. The terminology used originally and appearing on the software interface is listed below:

I. ***Cycle time***
II. ***Number of cycles***
III. ***Baseline pressure***: pressure in the foot, ankle and calf cuffs can be pressurized simultaneously up to a certain baseline value (typically 20mmHg) before the cycle begins.
IV. ***Onset delay:*** time between the beginning of the cycle and the moment the cuffs start to fill with air
V. ***Dwell time:*** period during which the cuffs remain inflated
VI. ***Target pressure*** in each of the three cuffs and in the reservoir
VII. ***High and low tolerances*** associated with the pressures in the cuffs and the reservoir: they indicate the highest and lowest limits of which the pressures can vary. For example, a pressure set to 100 mmHg with low and high tolerances equal to 5 and 10 mmHg, respectively, can, in fact, shift from 95mmHg to 110 mmHg

A Doppler sensor was included in the second version of the IPC boot prototype to measure the change in blood flow in the popliteal vein. Doppler values were recorded for different compression pressure values. The bottom left corner of Figure 3.21 shows a graph simulating the course of a cycle. In the upper part, the interface displays the exact pressure in the chambers and the reservoir, and especially their current "state" (filling, at baseline pressure, at target pressure, discharging). On the right, the graphs show the pressures in the different parts of the device, as well as the Doppler signal (arbitrary value), as a function of time over a period of one cycle.

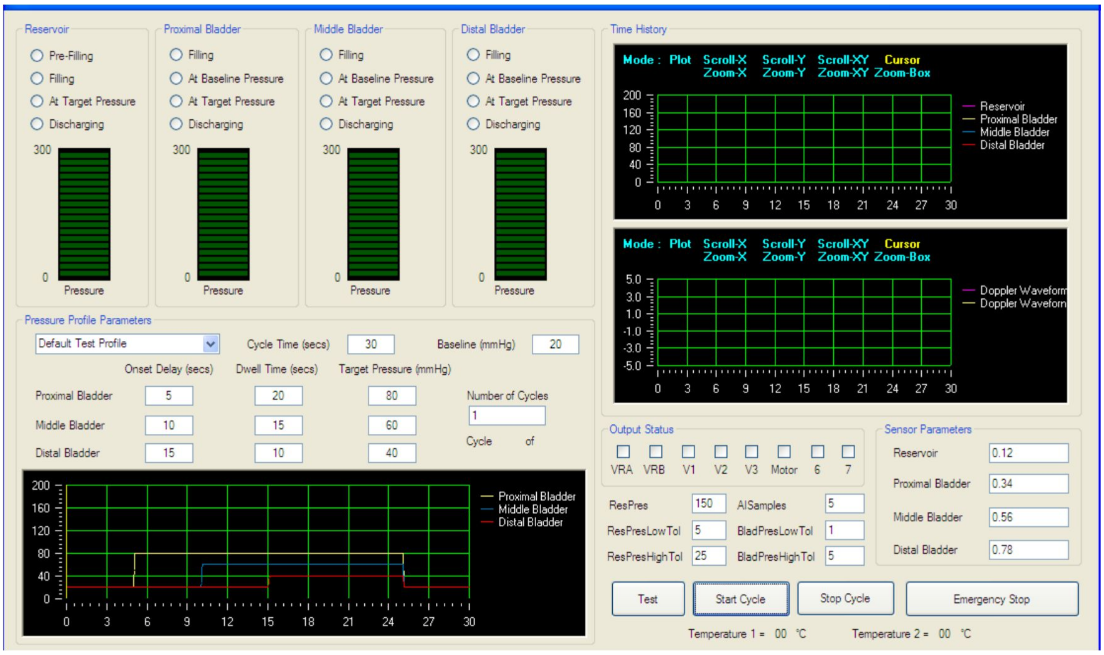


Figure 3.21: Control software for Version II IPC boot prototype

3.6.4 Reliability Tests on Version 2 IPC Boot Prototype

One of the first tasks before using the device was to complete a reliability assessment of the measurement of its parameters. Reliability tests were designed to ensure that the applied pressures by the device were indeed the ones appearing in the control software. For this purpose, the Pliance pressure measuring system (Novel, Munich, Germany), was used to assess, not only the magnitude but also the area of applied pressure on the participant’s leg during cuff inflation. The Pliance sensor system comes as a complete package of sensor mats in different shapes, cables, a wireless transmitter device, software, and computer.

The actual pressure applied to the limb (skin surface) was measured, using the Wireless Novel Pliance pressure measuring system, with the Elastisens S2073 and S2074 sensor mats and the Pliance X-32 software (novel Gmbh Munich).The actual applied pressure to the subject’s limb was checked using three different methods:

1. Electronic pressure sensors (Smartec SPD015GA)
2. Manual sphygmomanometer
3. Pressure sensor mat Elastisens, (Novel Gmbh, Munich, Germany)

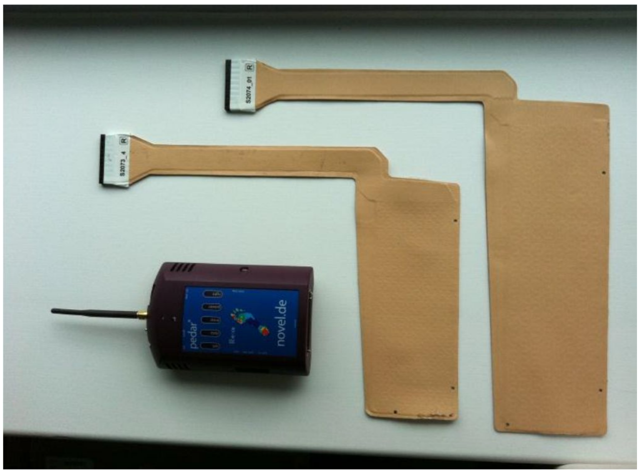


Figure 3.22: Pressure measuring system, consisting of the Pliance Sensor mats, X-32 software and wireless transmitter (Novel Gmbh, Munich, Germany)

Two Pliance sensors of different surface areas were chosen to test real time pressure application on a participant's calf and ankle during a session of prototype testing. The pressure values obtained from the Pliance systems (Figure 3.2.3) were compared with those measured by the sphygmomanometer and electronic sensors to determine the reliability of the pressure values recorded by the sensors.

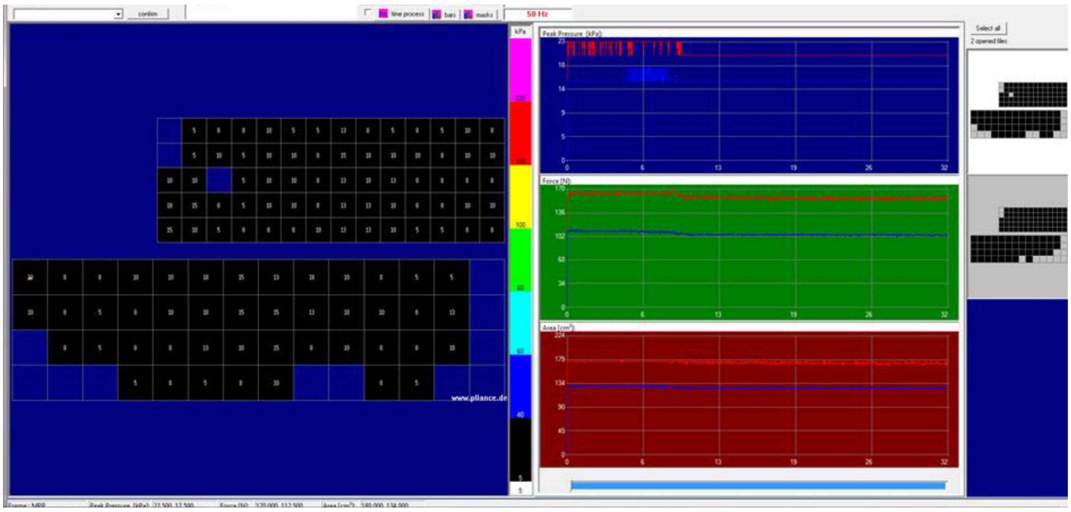


Figure 3.23: Pliance software interface. Dark: areas of low pressure. Purple: areas of high pressure.

3.6.5 Pressure Sensor Testing Protocol

Five healthy participants fulfilling the inclusion and exclusion criteria, listed later in this chapter, were explained the procedure and recruited after they gave their informed consent for testing. Ethical approval had been granted for testing as per the University's policy.

The two pressure sensors were attached circumferentially to the participants' lower and upper calf areas, using adhesive tape. All testing was performed with the subjects sitting. Once the sensors were secured the participant wore the device. An analogue manometer (Figure 3.24) was attached to the second tubing of the cuffs in order to display the cuff pressure values. The manometer pressure values were then compared with pressure measurements obtained from the Pliance sensors (Figure 3.25). The target pressures were set on the software device and the cuffs were inflated.

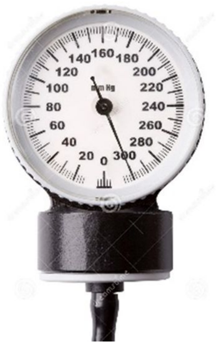


Figure 3.24: Analogue manometer fixed to the cuff tubing to confirm pressure measurements.

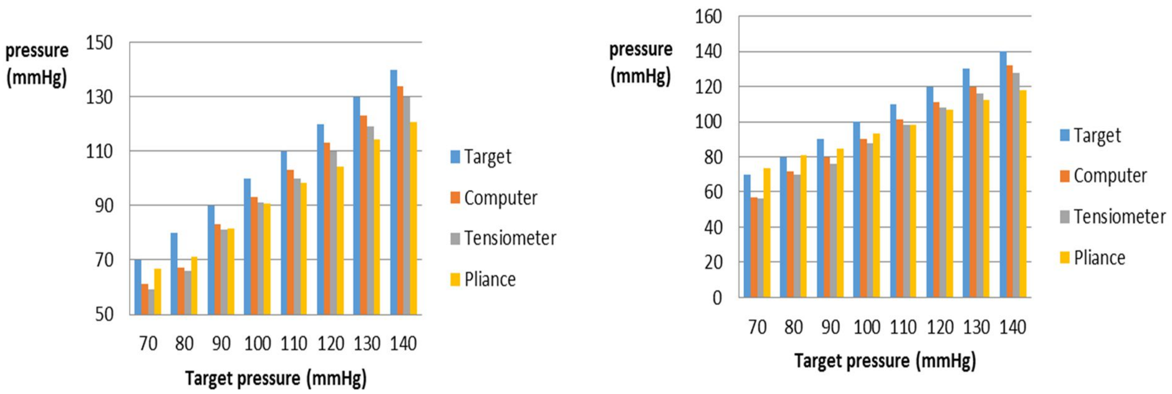


Figure 3.25: Comparison of the pressure readings from (i.) the controlling software (target), (ii.) electronicc valves, (iii.) manometer and (iv.) Pliance pressure sensors

Although the absolute values target pressures are different from the pressure measured with sensors on the participant’s skin, the comparative values remained statistically insignificant and the trend in values was comparable.

Subsequently, the second version IPC boot prototype was tested on five participants, using the following settings shown in Table 3.5.

Table 3.5: Control settings during data collection

Parameters	Settings
Compression mode	Sequential
Compression grading	Three cuffs, foot, ankle, calf: 120/100/80 mmHg
Compression frequency	2 compression cycles per minute
Length of compression cycle	15 seconds
Length of deflation period	15 seconds
Magnitude of cuff pressure	120/100/80 mmHg
Length of time of individual cuff compression	15/10/5 seconds (distal/middle/proximal cuff)
Time required to achieve target cuff pressure	How fast the cuffs are inflated
Use of baseline (background) compression	35 mmHg

During the first trials of the second version of the IPC boot prototype, it was observed that the real pressures were systematically lower than the set pressures (Figure 3.26). The reason for this was that the tolerances associated with the pressures in the bladders were too high. After modifying the tolerance values and opting for smaller tolerances, the pressures reached the target, but then dropped sharply (Figure 3.26b). In fact, the valves endeavored to maintain the pressures in the cuffs as close as possible to the targets (within the boundaries imposed by the tolerances). Hence, they opened and sealed incessantly, resulting, paradoxically, in air losses and fall in pressure. Since there wasn't any immediate solution to remedy the discrepancies in pressure values, special attention was given to the actual pressures (given by the software Boot Control) when using the device (Figure 3.26c).

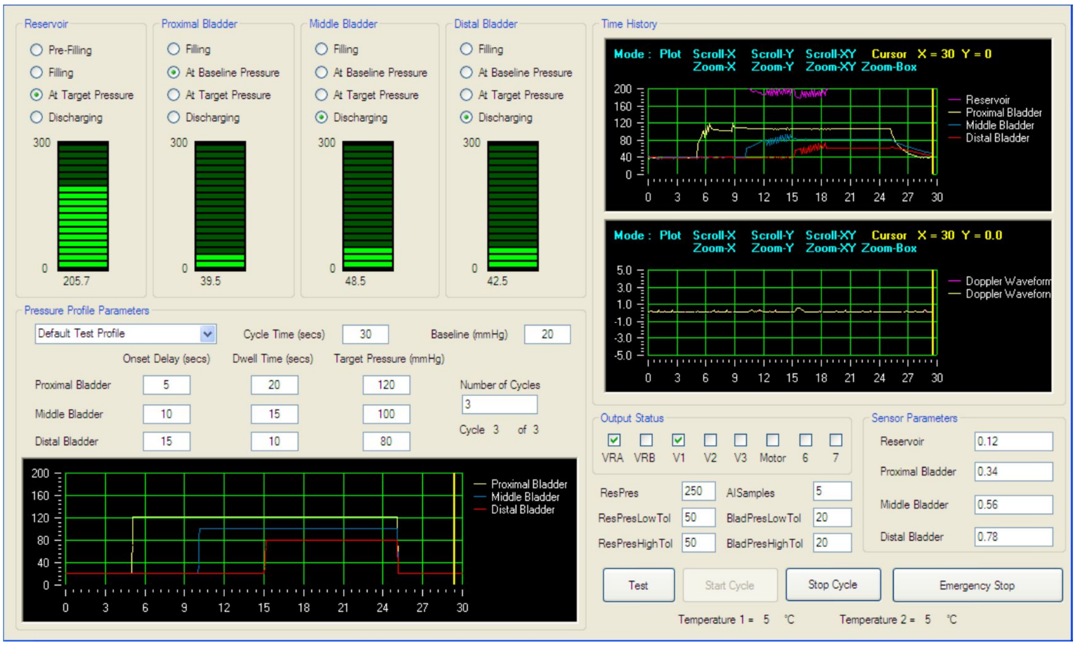


Figure 3.26a: Display of IPC cuff pressure values, showing discrepancies between target and actual pressures values (target pressures: [120 – 100 – 80] mmHg, actual pressures: [105 – 80 – 60] mmHg)

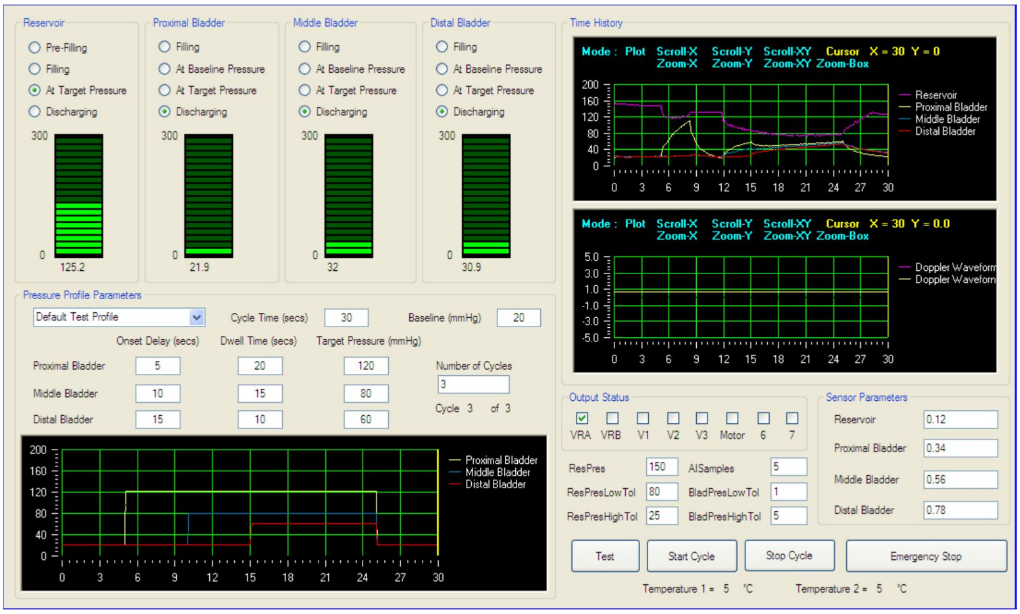


Figure 3.26b: Display of IPC cuff pressure values with smaller cuff tolerances, showing lower discrepancies between target and actual pressure values, but a drop in pressure

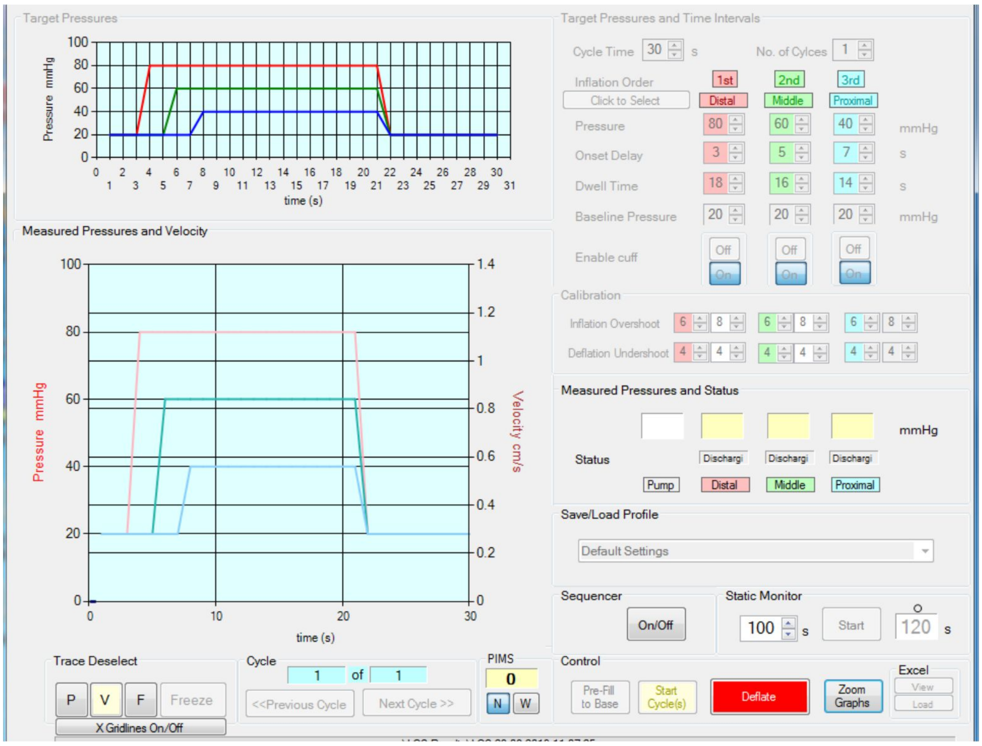


Figure 3.26c: The alternative interface of the controlling software LCS (Leg Compression System) for Version II prototype. The interface was more user-friendly, with larger graph areas, clearer sub-screens, and more real-time function information.

3.6.6 Investigation of Optimum Pressure Range for Different Cuff Combinations

Preliminary tests were conducted by changing the following three parameters: the pressures in the inflatable cuffs, the position of the subject (standing, sitting, lying) and the number of active cuffs (one, two or three). The aim of this phase was to investigate changes in blood flow following the variations in parameters. This would then help to determine the protocol to apply during the large-scale testing. The first objective was to define a range of pressures that would have the best impact on the blood circulation. Six sets of pressures were staggered from [80 – 60 – 40]5 to [150 – 130 – 110] for C1-C2-C3 (Table 3.6).

Table 3.6: Sets of pressures used for version II prototype

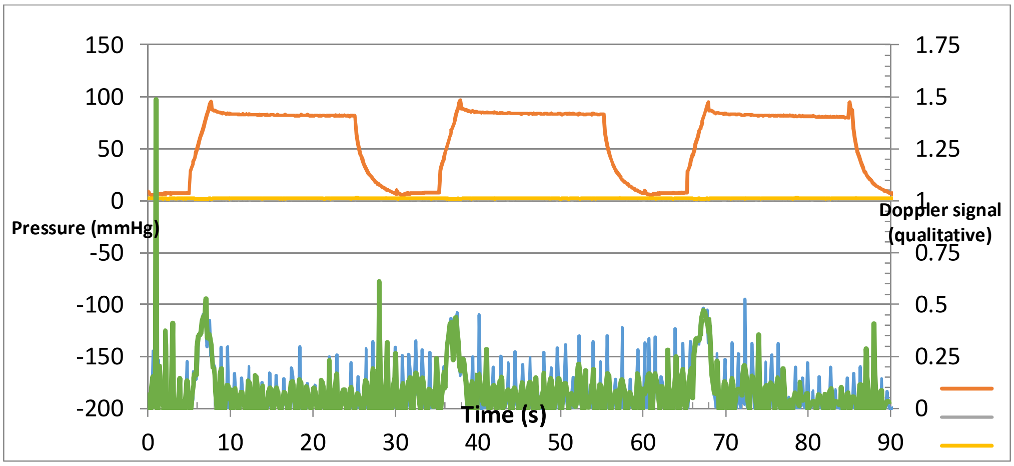
Pressures (mmHg)	Position	Actual Pressures (mmHg)	Reservoir Pressure (mmHg)	Baseline (mmHg)	Reservoir Tolerances (mmHg)		Bladder Tolerances (mmHg)	
					Low	High	Low	High
80 - 60 - 40	Standing / Sitting	70 - 50 - 30	150	20	30	30	8	8
100 - 80 - 60	Standing / Sitting	85 - 65 - 45	180		30	30	5	20
110 - 90 - 70	Standing / Sitting	95 - 70 - 50	200		50	50	10	20
120 - 100 - 80	Standing / Sitting	105 - 85 - 62	230		50	50	10	20
140 - 120 - 100	Standing / Sitting	115 - 95 - 70	270		60	60	20	30
150 - 130 - 110	Standing / Sitting	125 - 100 - 80	270		60	60	20	30

To investigate the effect of different cuff combinations on blood flow, the system was operated using one chamber at a time and in the same conditions of the actual pressure, in order to determine if one cuff of them was more effective than the other. Similarly, the tests were performed for combinations of two cuffs, as shown in Table 3.7.

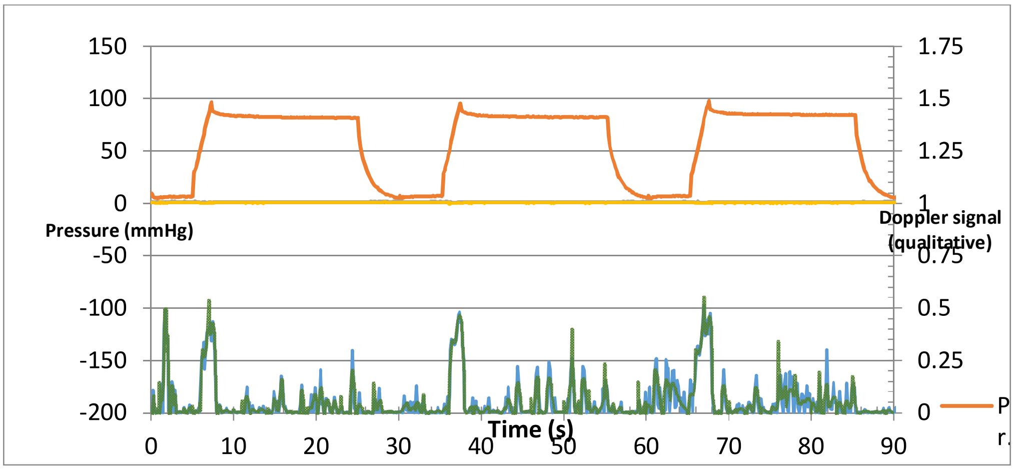
Table 3.7: Combinations of bladders tested using Version II IPC boot prototype

Cuffs		Position	Target pressures (mmHg)	Actual Pressures (mmHg)	Reservoir Pressure (mmHg)	Onset Delay (s)	Dwell Time (s)	Baseline (mmHg)	Reservoir Tolerances (mmHg)		Bladder Tolerances (mmHg)	
									Low	High	Low	High
One Cuff	**Foot**	Standing / Sitting	100	85	180	5	20	20	30	30	5	20
	Middle	Standing / Sitting	100	80	230				50	50	10	20
	Upper Calf	Standing / Sitting	100	80	250				50	50	10	20
Two Cuffs	**Foot & Middle**	Standing / Sitting	110 - 100	100 - 80	250	5 - 10	20 - 15	20	50	50	10	20
	Foot & Calf	Standing / Sitting	115 - 100	100 - 80	250				50	50	10	20
	Middle & Calf	Standing / Sitting	120 - 100	100 - 80	250				50	50	10	20

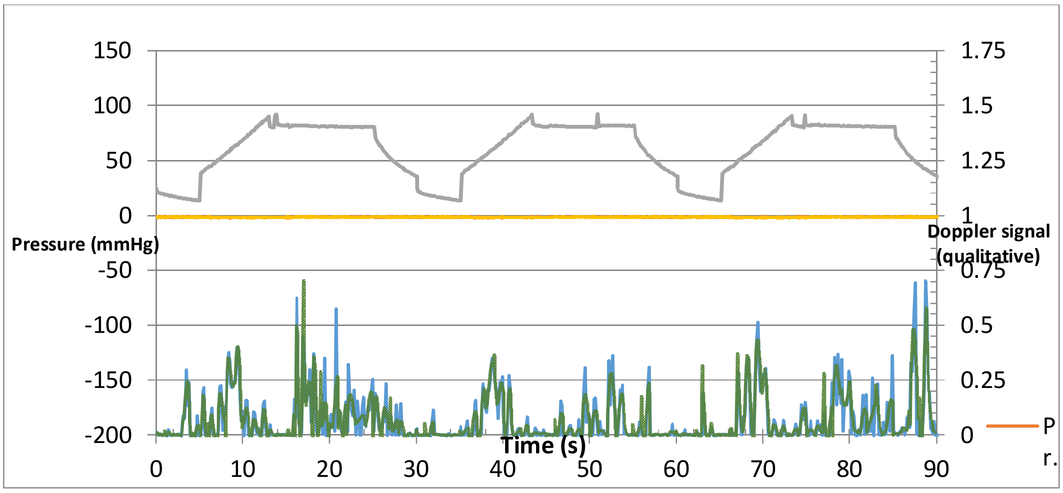
The experiments were repeated for all three basic positions, standing, sitting, and lying (Tables 3.6 and 3.7). The tolerances also had to be modified to get the most stable pressures. This, however, did not affect the results, since the aim was to investigate the relationship between the Doppler signal and the actual pressures. The protocol adopted all along the testing was relatively simple. The participants would put on the boot, position the probe that would be maintained at the right place, utilising an elastic strap, and finally sit, stand or lie down. Subsequently, each test lasted 5 x thirty-second cycles. The first two cycles were used only to stabilise the pressures and the corresponding data were not included in the data. Ten trials were conducted for each set of parameters, removing and replacing the probe between each trial. That accounted for 360 tests overall.



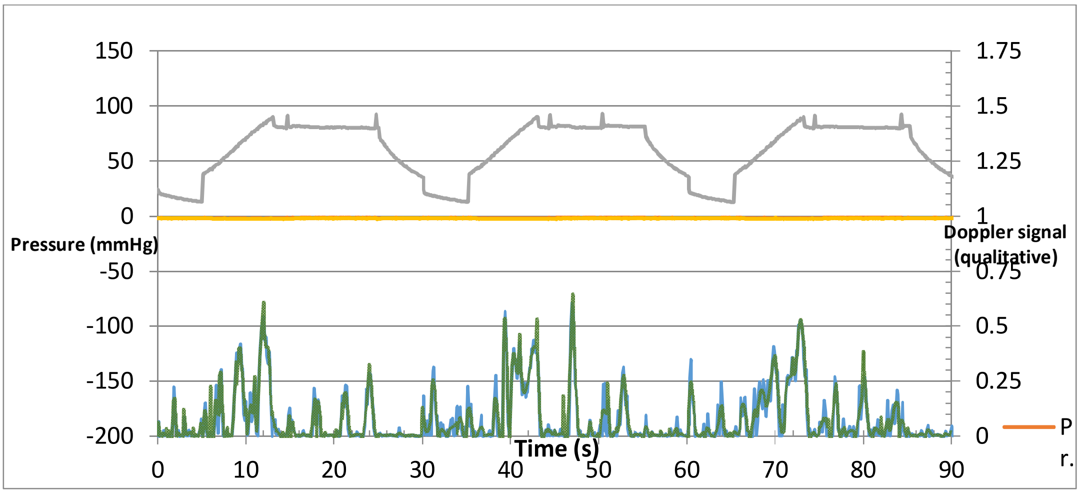
Testing Variations – Number of Cuffs, Pressure applied and Doppler signal acquired
Cuff Pressures: 100-80mmHg,
Number of Cycles and Cycle duration: 3x 30s cycles,
Number of Cuffs: Single cuff, Foot cuff,
Body Position: sitting still – knee flexed at 45°



Testing Variations – Number of Cuffs, Pressure applied and Doppler signal acquired
Cuff Pressures: 100-80mmHg,
Number of Cycles and Cycle duration : 3x 30s cycles,
Number of Cuffs: Single cuff, Foot cuff,
Body Position: standing still – knee slightly flexed



Testing Variations – Number of Cuffs, Pressure applied and Doppler signal acquired
Cuff Pressures: 100-80mmHg,
Number of Cycles and Cycle duration: 3x 30s cycles,
Number of Cuffs: Single cuff, ankle (middle) cuff,
Body Position: sitting still – knee flexed at 45^{o}



Testing Variations – Number of Cuffs, Pressure applied and Doppler signal acquired
Cuff Pressures: 100-80mmHg,
Number of Cycles and Cycle duration: 3x 30s cycles,
Number of Cuffs: Single cuff, ankle (middle) cuff,
Body Position: standing still – knee slightly flexed

3.6.7 Venous Blood Flow Assessment

The miniature Doppler probe was positioned, with the aid of an elastic band, in the popliteal fossa, over the popliteal vein. The difficulties encountered with positioning the Doppler into place included (i) identifying the optimal location of the Doppler probe placement and (ii) obtaining clean venous signals, with high signal to noise ratio. The Doppler sensor placement method used in this study overcame the above two major challenges and, therefore, permitted the evaluation of the effectiveness of the different applied compressions.

The popliteal vein is anatomically located right next to the popliteal artery in the popliteal fossa. The arterial signal is much stronger and easier to trace than the venous signal. Hence, the Doppler probe was positioned, first, by identifying the artery and then by placing the probe just laterally to popliteal artery. The Doppler signal obtained would inevitably contain, both, venous and arterial signals. The venous signals would not be audible, unless when compression was applied on the calf or when the subject flexed their calf muscles.

The mixed venous and arterial signals were filtered, using a Fourier analysis of the waveforms to obtain a new waveform containing Doppler data for the venous flow only by removing the arterial waveform with a typical repeating spike pattern. The resulting smooth waveform represented blood velocity in the popliteal vein only (Figure 3.40).

The Doppler signal does not give the absolute value for the velocity of blood flow so the data collected were considered to have an arbitrary unit (AU). The amplitude of the filtered venous waveform increased with increase in external compression pressure values. The filtered Doppler waveform for the venous flow (representing blood flow velocity) for each cycle had multiple peaks. The area under velocity-time graph for the three peaks combined represents distance travelled in an arbitrary unit, referred to as stroke distance.

$A = V.t$

$V = S/t$, represented by the Doppler arbitrary values

$A = (S/t).t$

$A = S$

Where A: area under velocity-time graph, V: velocity, S: distance, t: time

3.6.8 Repeatability Tests and Preliminary Data Analysis

The Boot Control software was designed to produce an excel sheet for each operating cycle. One file contained six columns, giving the numerical values for a time in the cycle, reservoir pressure, distal cuff pressure, middle cuff pressure, proximal cuff pressure, and Doppler signal.

Values for the last three of the five cycles of the same test were downloaded to a single excel file, where a new column was inserted for time for the three cycles. This resulted in one file for every 360 tests. Since the pumping mechanism was, however, not equipped with a timer, the numerical values for the pressures and the Doppler signal were not synchronised, making them incomparable from one test to another.

To remedy this, an excel macro software was developed that would model the ultrasonic signal as a polynomial of degree six, hence enabling to assess a value every 0.1 seconds, from 0 to 90 seconds (three cycles). Using this technique, it was possible to display the graphs of the Doppler signals as functions of time, all of them with the same normalised x-axis (Figure 3.27).

The baseline Doppler signal was a continuous low volume and high-frequency noise that was filtered out.

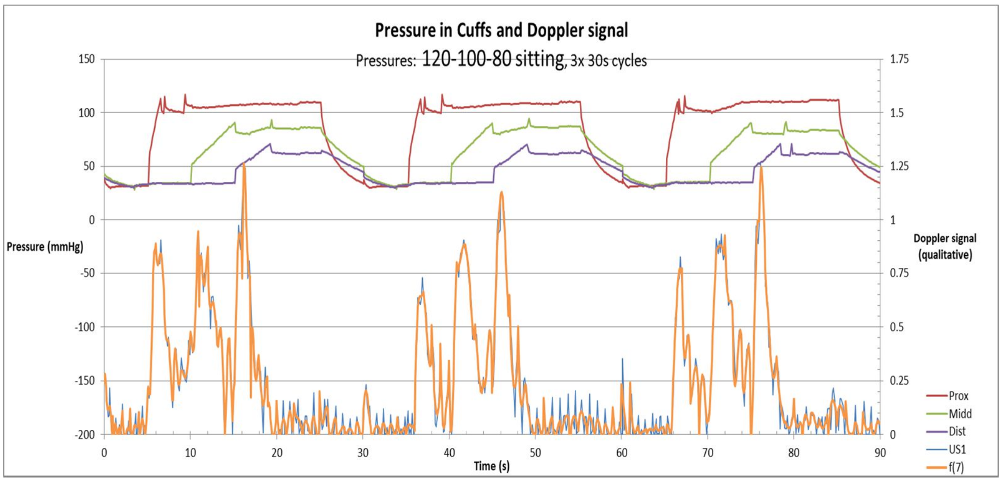


Figure 3.27: Graph showing the cuff pressures and Doppler arbitrary values, modelled by a polynomial of degree six against time for three 30-second cycles with target pressures of [120 – 100 – 80] mmHg, sitting.

Finally, each series of ten tests were run with the same set of parameters, the time-axis was normalised and the results were averaged and plotted against normalised time. Figure 3.28 shows one of the 36 graphs produced from the repeatability tests.

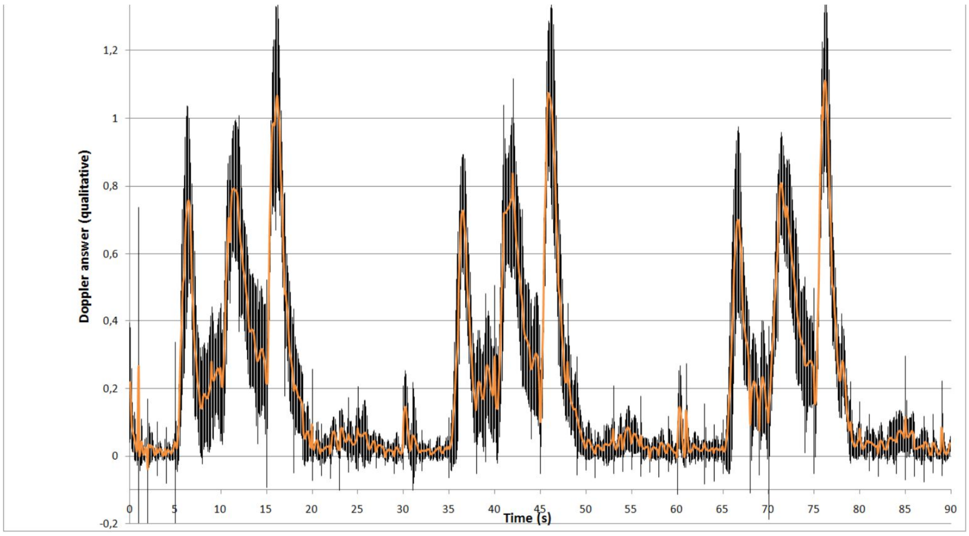


Figure 3.28: Average Doppler values (Arbitrary Units) over ten tests performed with target pressures of [120 – 100 – 80] mmHg, sitting, 3x30 cycles

It was noted that there was a general decrease in pressure during the second trial. This decrease in pressure was very prominent in nine of the twelve testing series (Figure 3.29). This is likely to be inherent to the pumping mechanism, probably affects the averaged Doppler signal.

Figure 3.29: Spaghetti plot of total pressure values of the proximal, middle and foot cuffs for each trial in the order they were recorded.

The standard deviations and variation coefficients values for the different series also demonstrate the lessened consistency of the results. Based on these results, data from the second cycle were discarded from future analyses.

3.6.9 Importance of Sufficiently High Pressures and Role of the Foot Cuff

The first obvious observation was that the data results of the lying position testing were not usable (either no signal or very large signal to noise ratio, even when the test had not begun yet). A possible explanation of this could be that when the leg was stretched out horizontally, the veins were partially empty. Thus, the pressure required to force the blood through the vessel and produce a traceable Doppler signal was much higher than during standing and would be unbearable. A potential solution could be a slight knee flexion (e.g. 30^{o}) which would allow easy access of the Doppler probe into the popliteal fossa and possibly allow better signal acquisition in combination.

Regarding pressure variations, the graphs in the Appendix show two or three noticeable peaks along the Doppler waveform. The parameters used to compare the different graphs are (i) the maximum value of each peak, (ii) the time taken to reach the maximum value of each peak in the cycle and (iii) the area under each peak. The peaks are evidently the consequence of cuff inflation. Figure 3.30 displays the time at which the maximum value of each peak was reached in the cycle for all six sets of pressures, standing and sitting positions grouped together.

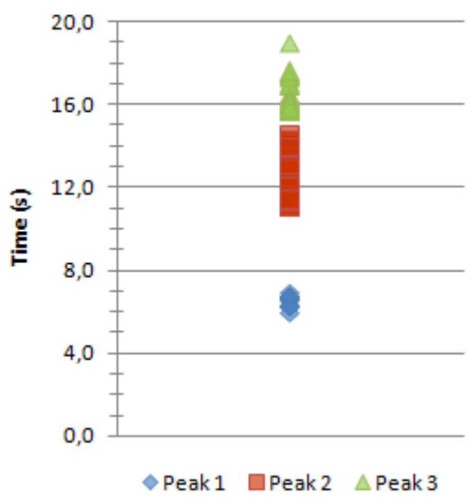


Figure 3.30: Time at which the maximum value for each peak Doppler value was reached in the cycle

The times to reach the maximum values for peak 1, peak 2 and peak 3 are in the intervals [5.9 – 6.9], [11.0 – 14.5] and [15.7 – 19.0] seconds respectively. Thus the peak values arise just after the cuffs began to fill. These values correspond to the onset delays that were set to 5, 10 and 15 seconds). This proves that the first, second and third peak values result from the inflation of the foot, ankle and calf cuffs, respectively. The reason why the response time between the onset delay and the Doppler values is longer for the ankle and calf cuffs is that these cuffs are larger in volume compared to the foot cuff and, hence, take longer to inflate.

The area under the Doppler curve and, more particularly, under the peak areas, is a meaningful value. When multiplied by the cross-sectional area of the popliteal vein, the volume of blood flow rate through the vein can be estimated. Assuming a constant diameter (and hence the cross-sectional area) for the popliteal vein for all pressures, the area under the curve for the Doppler values is proportional to the flow rate. The Doppler values in this study are arbitrary stroke distance values. If calibrated, values for velocities could be obtained. The areas under the curves, although having arbitrary units, could be compared to the peak pressure values.

3.6.10 Preliminary results

Standing

Overall, when the pressure-time integral in the cuffs increased, the values for the total area under the Doppler waveform (the stroke distance) also increased (Figure 3.31).

Common trends were observed for the area under the Doppler arbitrary value curves for each maximum peak pressure value set:

I. Stroke distance for the first peak was negligible for the different maximum peak pressure values.

II. The third peak was higher than the second one, irrespective of the maximum peak pressure values.

The significance of these results is that the proximal cuff has a higher contribution to increasing blood flow than the middle cuff. The distal cuff did not contribute to increase in blood flow (Figures 3.32, 3.33). Figures 3.32-3.36 also show that the optimum peak pressure value to stroke distance ratio for standing is the [110 – 90 – 70] mmHg peak pressure value set.

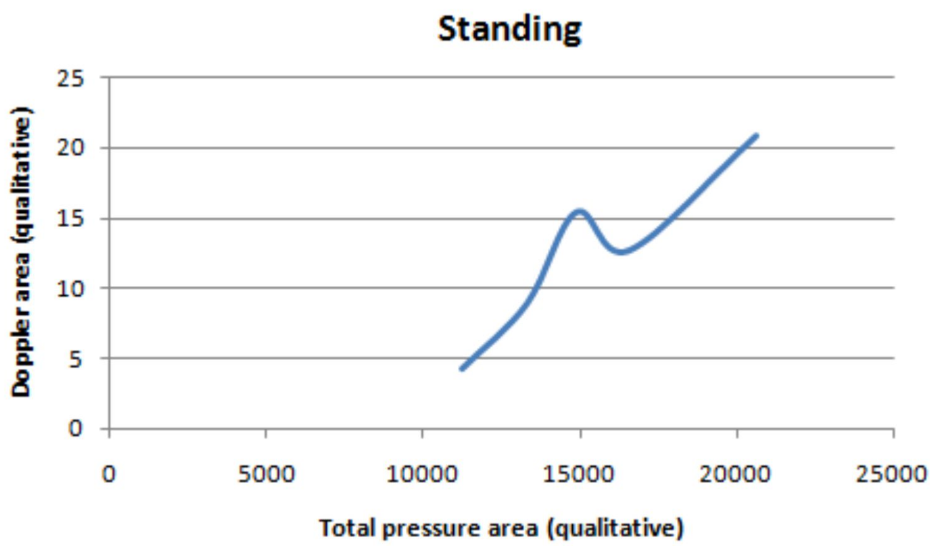


Figure 3.31: Influence of the pressure-time integral on Stroke distance while standing. The total pressure area is the sum of the areas under the curve during a compression cycle on a pressure over time graph (Fig 3.27).

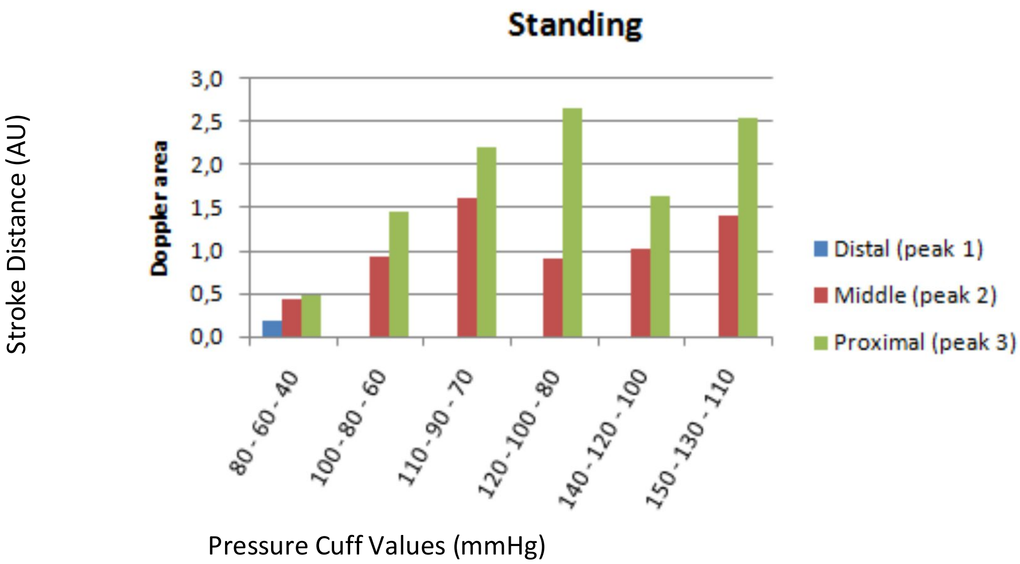


Figure 3.32: Effect of different sets of peak pressure values on Stroke Distance contributed by each cuff when standing - two individuals, multiple repeatability tests – analytical data in appendix

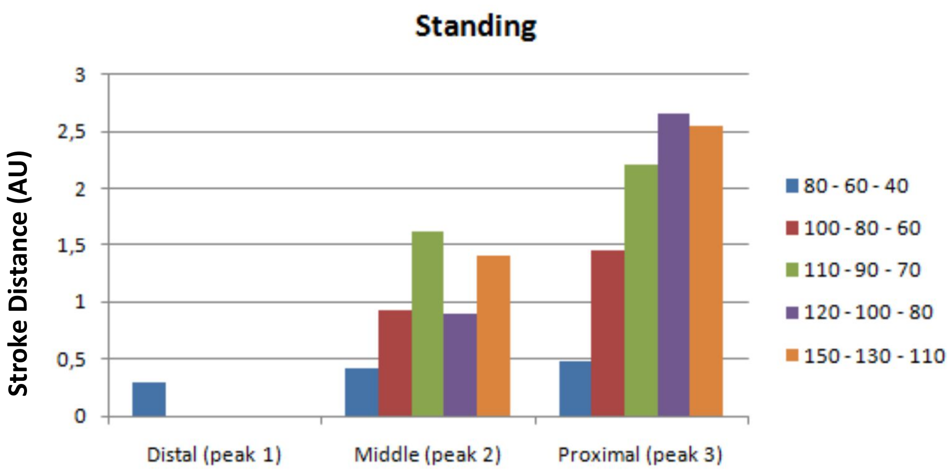


Figure 3.33: Effect of different cuff peak pressures on Stroke Distance when standing – two individuals, multiple repeatability tests – analytical data in Appendix

Sitting

The same tests were conducted for the sitting posture and the results followed the same trend as those for the standing posture. In general, as the pressure-time integral in the cuffs increased, the stroke distance also increased (Figure 3.34).

Figures 3.35-3.36 show that for both individuals:

I. The optimum peak pressure to stroke distance ratio for sitting is the [120 – 100 – 80] mmHg peak pressure value set.

II. Stroke distance for the first peak was negligible for the lower peak pressure values of 80 and 100 mmHg.

III. In general, the second and third peaks were higher than the first one.

IV. Unlike the standing position, sitting is characterised by an enhanced effect of the ankle cuff compared to the calf cuff, at least for high pressures.

V. The contribution of the foot cuff is visible for the sitting posture.

VI. The stroke distance measured for the pressure sets 140/120/100 and 150/130/110mmHg did not increase as it did with the lower pressure sets (Figure 3.35). This paradox may be explained by the limitations of the device's pump which struggled to achieve and maintain such high pressures. As a result, the inflation time for the particular cuff was ended before the - high – cuff pressure was actually achieved.

The significance of these results is that the proximal and middle cuffs contribute most to increasing blood flow than the distal cuff. The distal cuff did not contribute to increase in blood flow (Figures 3.35-3.36).

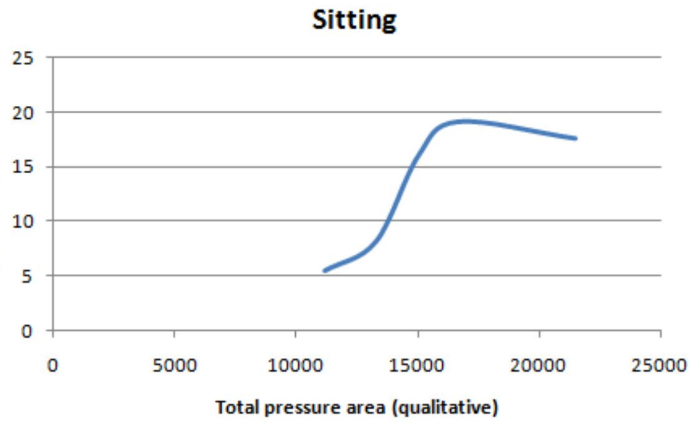


Figure 3.34: Influence of the pressures applied when sitting

This trend is confirmed by examining the three peaks independently, even though an exception arises for the foot cuff.

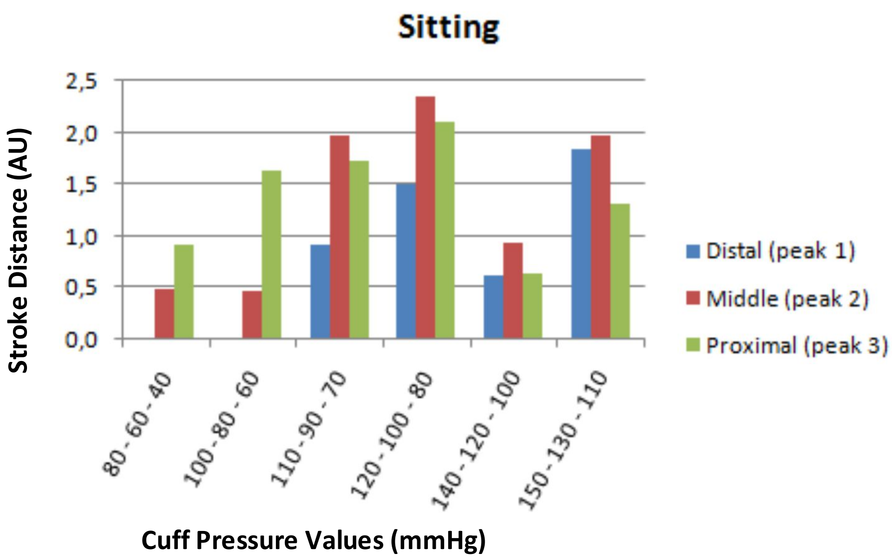


Figure 3.35 Comparison of Stroke Distance with regard to the cuff inflated when sitting - two individuals, multiple repeatability tests – analytical data in Appendix

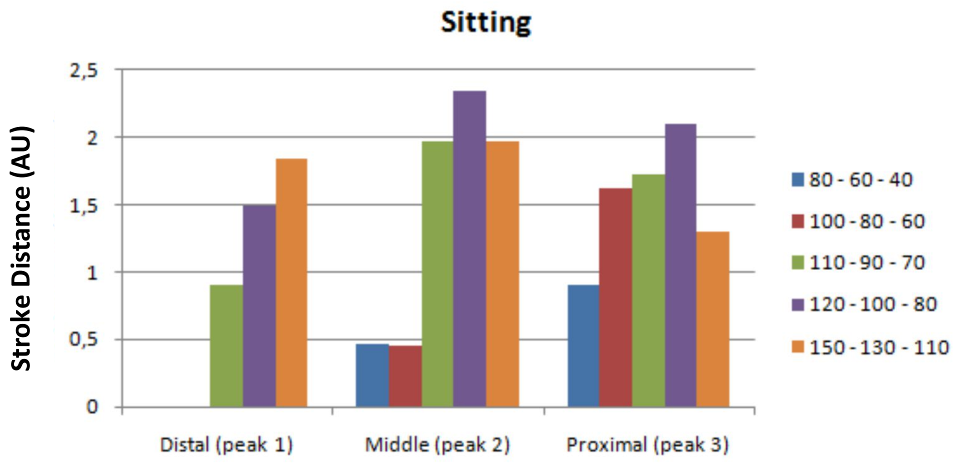


Figure 3.36: Comparison of the Doppler area for different pressures when sitting - two individuals, multiple repeatability tests – analytical data in Appendix

The results are relatively similar when standing or sitting, with one or two exceptions. The three cuffs tested separately, each produced one peak for stroke distance. Their maximal values were very close. However, the calf cuff generated a wider peak for stroke distance than the ankle and the foot cuffs (Fig 3.27). The action around the upper calf was more progressive and slower as that is a large cuff – this may explain the difference in the Doppler waveform acquired. The area under the Doppler value curve with time (stroke distance) is higher for the ankle cuff when standing, but higher for the calf cuff when sitting (Figure 3.37). This phenomenon may have to do with the venous pressure against which the cuffs have to act. In the case of a sitting individual the ankle cuff acts against a lower pressure gradient and hence can be more effective. On a standing up subject the cuff action is more cumulative and the higher (proximal) cuff receives a larger volume of blood which will have to propulse.

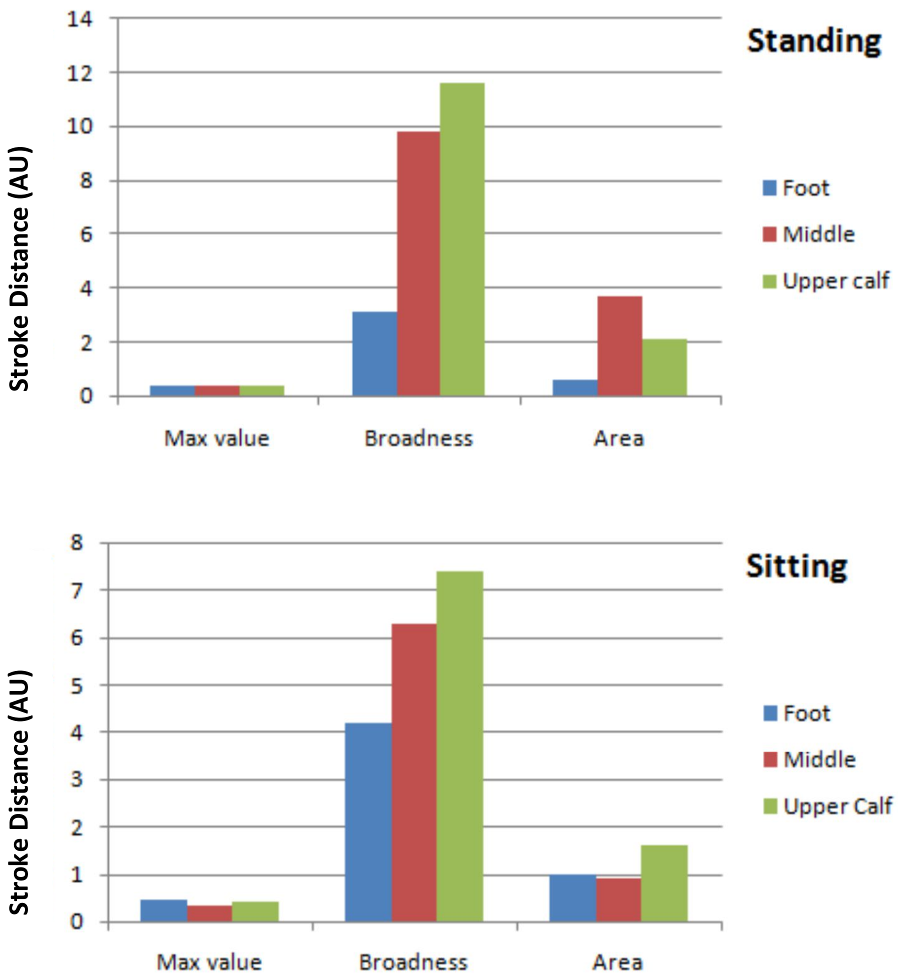


Figure 3.37: Properties of the Doppler waveform corresponding to each cuff tested alone when (top) standing and (bottom) sitting – Analytical data in Appendix

Comparing the Doppler results for the ankle cuff alone and combined with the foot (using the same pressure for the ankle cuff) indicates that the foot cuff is clearly not of any help to the ankle cuff and seems to even lessen its action (Figure 3.38). This can be deduced by the maximum value of the peak corresponding to the ankle cuff. The area and broadness of the peak cannot be compared due to different onset delays and dwell times. It is unclear why the foot cuff does not significantly contribute to this combination of cuffs.

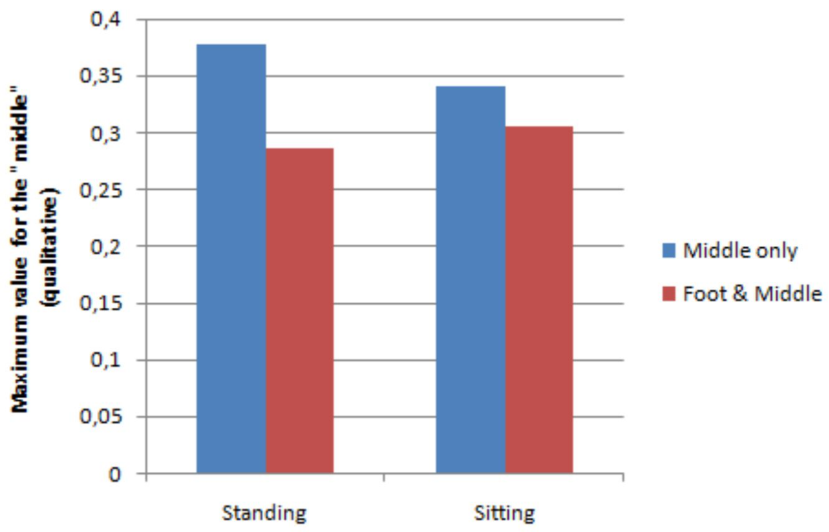


Figure 3.38: Influence of the foot cuff on the action of the ankle cuff – Analytical data in Appendix

Effect of the foot cuff on the performance of the proximal and middle cuffs

Figure 3.39 shows that the foot cuff leverages i) the impact of the calf cuff alone, as well as ii) the combined effect of the calf and ankle cuffs on the change in blood flow.

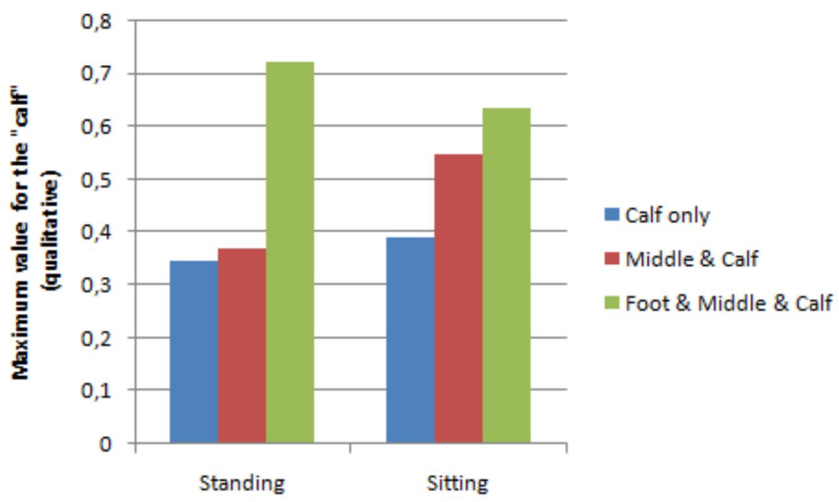


Figure 3.39: Influence of the foot cuff on the action of the ankle and calf cuffs

Although the effect of the foot cuff alone on the change in blood flow is not noticeable, it seems to enhance the effect of the other two cuffs on the change in blood flow. A possible explanation is that the foot cuff augments blood flow towards the calf, creating a priming effect for the ankle and calf cuffs. The use of the foot, ankle and calf cuffs appears to be the best combination. The contributions of the different cuffs on the change in blood flow at different pressure levels were generally similar during standing and sitting. The prototype IPC boot was not effective in the supine position.

Stroke Distance

The present research utilises stroke distance which is routinely used in echocardiography. Stroke distance was measured in real time during the course of IPC using a Doppler device. Stroke distance is measured over the length of one compression cycle and is used extensively in this thesis as a measure of the haemodynamic change in the popliteal vein assessed by the Doppler device. Stroke distance is the product of velocity and time (Velocity-Time Integral (VTI) - the area under the curve) in an arbitrary unit. The measurable outcome in this study is the relative flow change and not the absolute value, hence, the use of arbitrary units is justified.

The lowest set of pressure chosen was 80/60/40 mmHg for the foot/ankle/calf cuffs. The values are based in the knowledge that, for a healthy adult of average height and standing up, the venous pressure at the level of the foot/ankle is approximately 90 mmHg falling to 40 mmHg at the level of the lower thigh (Guyton 2015). Tests were also conducted with two more sets of pressures: 100/80/60 mmHg and 120/100/80 mmHg. Although none of the participants had a history or symptoms of peripheral vascular disease, these pressures were not exceeded. The deflation times used were 10, 20 and 30 seconds.

Figure 3.40 is a representation of a compression cycle with the recorded waveform curve of venous blood velocity over time. The area under the curve represents the velocity-time integral or stroke distance. The area was defined by using Fourier transform. The sum of the stroke distances (VTI1+VTI2+VTI3 in Figure 3.40) over one compression cycle has been used as the main outcome measure in this research.

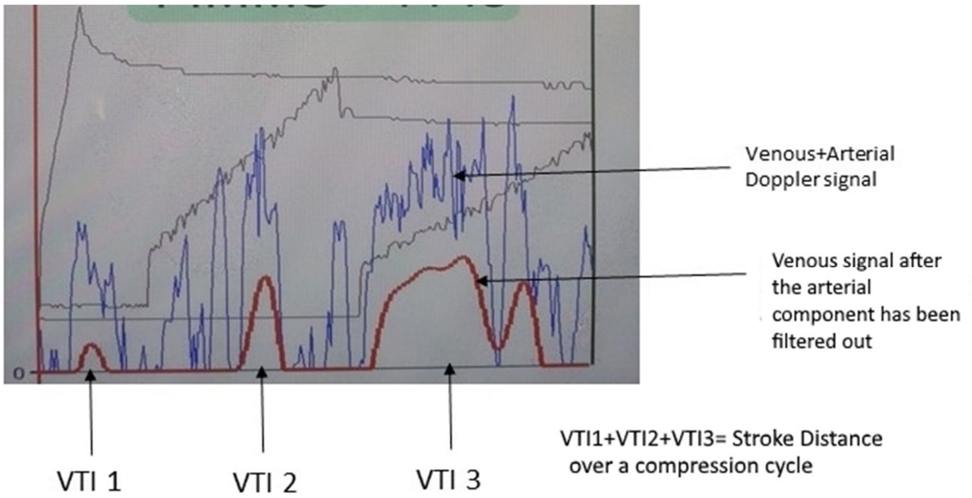


Figure 3.40: The filtered venous blood velocity waveform (red line), following the cuff inflation. Graphical representations of the computation of the collective velocity-time integrals (VTI1, VTI2, VTI3) and the total stroke distance in arbitrary value (AU). Here, the stroke distance is 1148 AU.

In order to calculate the velocity-time integral, the Doppler device output was used as the velocity signal output in arbitrary units. After the signal was retrieved, software routines were used to remove the high-frequency noise and signal components and to output the peak signal representing the venous return.

The total stroke distance is an arbitrary value representing the total area under the curve of the filtered waveform for one complete cycle. Successive total stroke distance values can be used as a measure of the change in blood velocity. The software displays the raw data in both tabular and graphical form.

Total stroke distance is calculated in routine SEQUENCER1 which processes 10 samples of raw data per second, determined by the Timer, tmrSequDisplay. At the end of each CYCLE, when all cuffs are deflated (routine DEFLATE TO BASE), the array of raw data as a function of time [TIMEARRAY()] is processed by the Fast Fourier Transform Library routine, FFT_LowPass, which performs the following:

1. Converts the signal to the Frequency Domain, where the high-frequency components can be removed. (Currently, values 0 to 11 of side frequencies are retained)
2. The d.c. level is adjusted. (Currently dc level = 0.2 units)
3. The signal is inverse transformed back to the time domain [LowPassTimeArray()]

The precise values for 1 and 2 are not critical but were chosen to give the most selective waveforms and also retaining positive values at all times for the type of raw data likely to be encountered. The resulting waveform identifies the position (time) and intensity of the peaks of venous return.

The area under the selected curve is then calculated and, using a suitable scale factor, total stroke distance, which is proportional to the area, is calculated automatically. As the area under the curve represents translocation (or distance travelled), the sum of the measured areas over the length of a compression cycle represents the distance that the blood has been shifted by.

The stroke distance is used, not only for data analysis to investigate optimum cuff pressures and the relative contribution of each cuff while standing, sitting and lying down, but also an arbitrary value for the real-time assessment of the applied compression. Stroke distance can be used in the device feedback mechanism to modify the compression parameters according to the subject's real-time needs. For example, if, while a subject is walking and the index values become high because of the function of the calf muscle pump function, the device operation will cease.

Currently, the software is set to compute stroke distance values over three compression cycles, calculate the average value for the three cycles and feedback to the controlling mechanism. If that average stroke distance value is below or above certain set values, the next cycle will start with higher or lower target cuff pressures.

Results obtained from the preliminary analyses were used to make an informed decision on the final prototype boot design, making it possible to explore further the effect of frequency, deflation and compression times on stroke distance. The Android software, used to compute stroke distance, can also calculate stroke distance from data obtained from previous versions of the device that used an older controlling software.

Three different versions of the prototype IPC boot device were used to. The compression produced from the exoskeleton, cuffs and tubing have not changed. Three repeatability and subject tests, using different compression profiles and body positions, were conducted. The prototype IPC boot allows an unlimited number of pressure settings and compression timings combinations. The initial tests were conducted, using settings cited in the existing literature for IPC. Upon completion of these initial tests, the parameters were changed to investigate the effect of different compression profiles on stroke distance to optimise the system.

The prototype boot control system is light and wearable and is very portable, as shown in Figure 3.41.

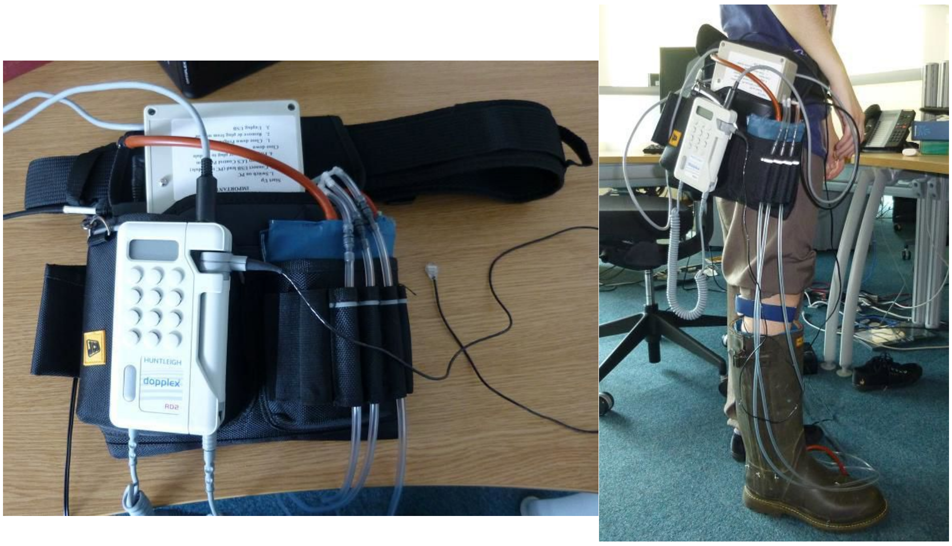


Figure 3.41: Left: The control box, Doppler sensor, and connection attached to a belt. Right: The device during testing, demonstrating its portability

3.6.11 Correlation of Stroke Distance with Duplex Ultrasonography

Synchronous real-time testing

One healthy participant was randomly chosen to undergo Venous Duplex examination of this popliteal vein during IPC with the prototype IPC boot. The testing took place in a Vascular Laboratory by an experienced sonographer. The prototype was worn and the Doppler probe was positioned, using the standard technique that was used for all participants. The participant was then asked to remain standing up, shift their weight to the contralateral leg and remain still with the leg under examination in a dependent position. The sonographer sat behind the participant and with the ultrasound probe in placed just above the Doppler probe. The IPC was initiated and the ultrasound waveform was stored for later assessment. The stroke distance values and waveforms, which are automatically stored in the portable device, were compared with the ultrasound waveforms (Figure 3.42). There was a strong visual correlation of the two waveforms both in terms of maximum peak and area under the curves.

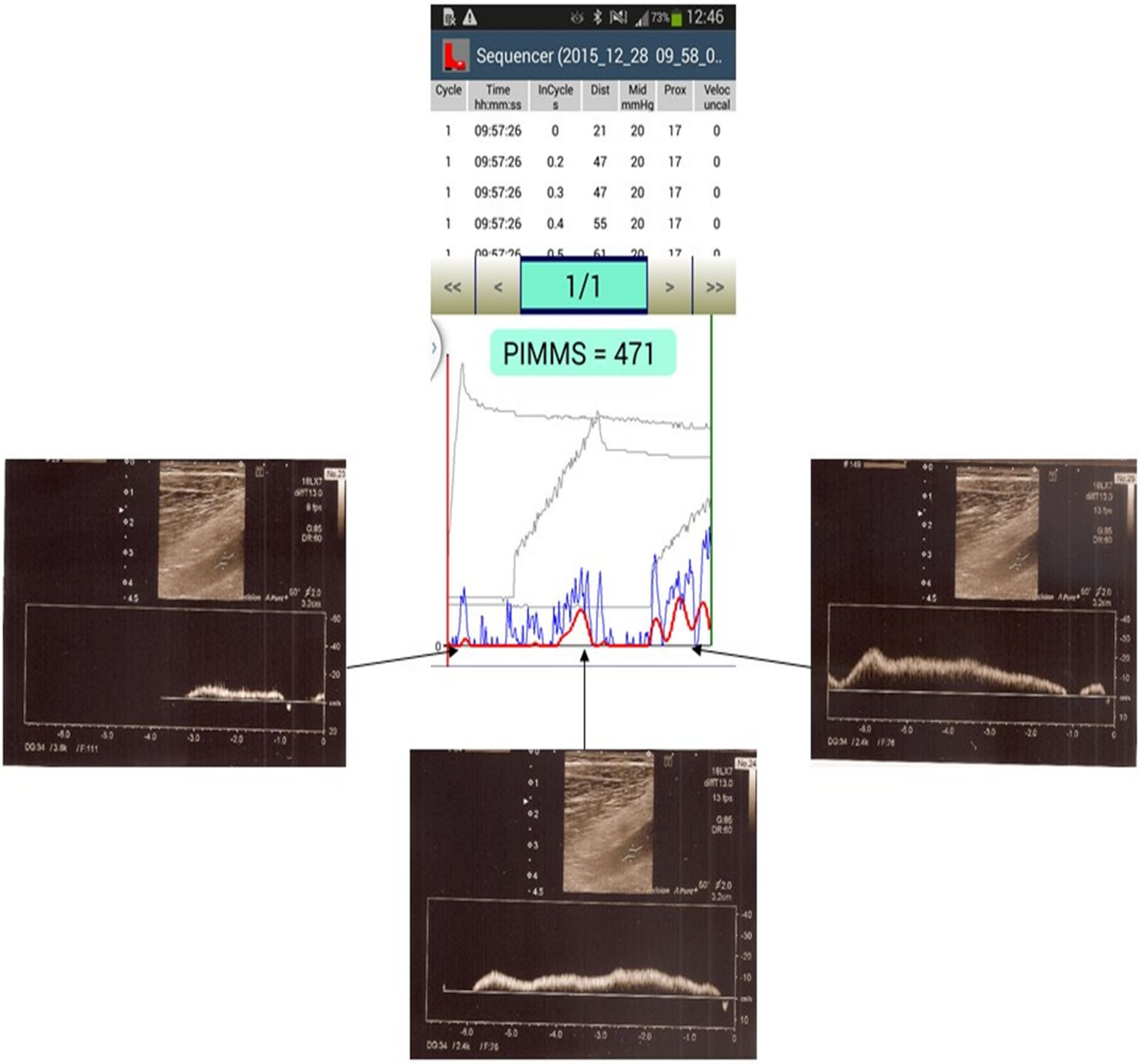


Figure 3.42: Real-time synchronous venous duplex and stroke distance assessment of the popliteal vein

3.7 Testing design

Ethics approval was applied for and granted for testing of healthy volunteers. A group of forty participants (twenty females and twenty males) was recruited after relevant invitation. The inclusion and exclusion criteria are listed in Table 3.7. The format of the testing and details of the procedure were explained to the participants prior testing. Informed consents were obtained on the day of testing.

Table 3.7: Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Healthy subjects Male or Female over 18 years of age	History of skin allergies
	Lower limb skin infection
	History of recent deep venous thrombosis
	History and/or symptoms of intermittent claudication
	Lower limb oedema caused by heart failure
	Inability to cooperate with testing
	Active leg ulcers
	Surgery to the lower limb during the previous 6 months
	Extreme leg/foot sizes (limited number of available prototype sizes)
	Unable to give informed consent

A typical test would start with the participant being welcomed to the Medical Engineering Research Group (MERG) at Anglia Ruskin University. Different times of the day were randomly assigned to participants. All participants were asked not to attend if they did not feel well or were feeling tired. The area temperature was controlled and kept between 20^{o}C and 23^{o}C.

The testing sequence was explained and mutually agreed upon prior consenting. All participants were asked to wear comfortable clothes that would allow exposure of their legs to the level of their lower thighs without compressing them. After exposure of their leg, they were given a single use non-compression stocking as a matter of hygiene. Testing was performed with the participant standing up with the leg under evaluation in a non-weight bearing position. Each test would take approximately sixty minutes, the participants were asked to shift their weight to the contralateral leg and use their arms for support by holding on the backs of two chairs parallel to each other. It was emphasised that it was important to stand still and avoid leg movements during testing.

Three different sizes of IPC boot prototypes were available and participants were offered the appropriate boot size. There were three different sizes of prototypes to satisfy differences of legs/feet sizes. The participants would then wear the prototype boot with the help of the supervisor who would place the flat Doppler probe in the participant's popliteal fossa. This was performed with the help of the Doppler device and the position was finalised when a biphasic or triphasic signal from the popliteal artery was obtained. The position would be confirmed by calf instant manual compression (squeeze) and tracing of venous flow audible on Doppler. The elastic strap bearing the Doppler probe would be secured around the leg.

Participants were asked to breathe slowly and any instances of a cough or movement were recorded. Testing started with a gradual increase of pressure to the level of 20mmHg which was labelled as resting pressure.

The decision to use resting pressure was made based on the following assumptions:

1. A nominal pressure of 20mmHg would fill the gaps between the exoskeleton and the participant's skin without compressing the veins. Partsch and Partsch (2005) showed that, in the upright position, an external pressure of 30 to 40 mm Hg is necessary to narrow the leg veins and a pressure of 70mmHg required to cause them collapse.
2. Higher pressures, especially in the case of low power mobile system, are faster achieved when the cuffs are pre-inflated. The importance for fast inflation was emphasised by Kamm (1986).

When the resting pressures were achieved, the device paused instantly and then the first compression cycle began. Testing was conducted, using three sets of pressures: 80/60/40, 100/80/60 and 120/100/80 mmHg, respectively, for the levels of foot/ankle/calf. Another variable was the deflation time, which represented the time between the deflation of all the cuffs at the end of one cycle and the onset of inflation of the foot cuff at the beginning of the next. The values used for the deflation times were 30, 20 and 10 seconds. Testing was initiated with the low set of pressures (80/60/40 mmHg) and long deflation times (30 sec) as this was considered a gentle to the participant introductory group of settings (Figure 3.43).

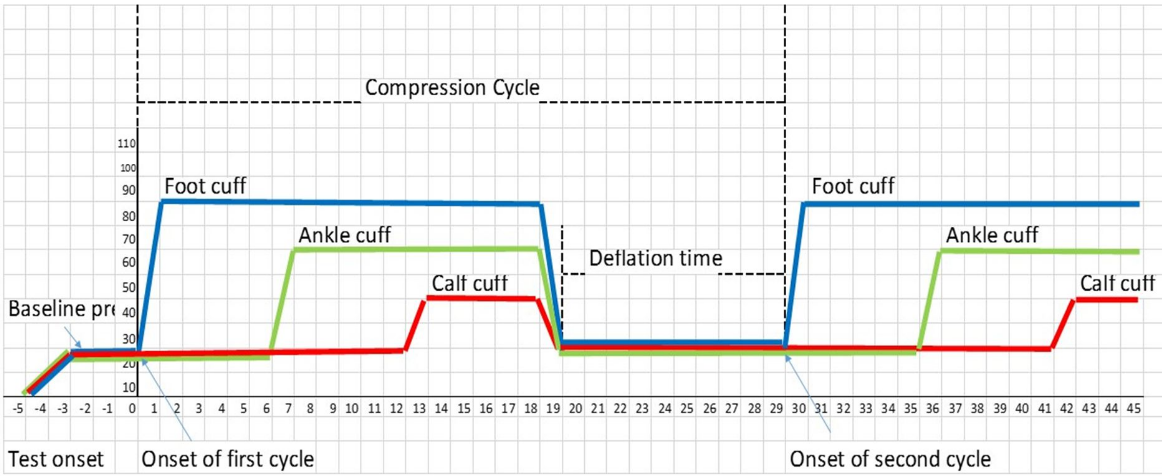


Figure 3.43: A typical compression cycle. The first cycle after the baseline pressures (20 mmHg) were achieved. The foot cuff is inflated first to a higher (80 mmHg) set pressure followed by the ankle (or lower calf cuff) to 60 mmHg and finally the upper calf cuff to 40 mmHg. All cuffs deflate simultaneously to baseline pressure and remain at that level of pressure for a pre-determined period of time (deflation period).

Choosing Sets of Target Pressures

Browse NR (1988), showed that during the transition from the supine to the standing position the foot venous pressure changes dramatically from 15mmHg to approximately 115mmHg as a result of the hydrostatic pressure that the column of blood (heart-to-foot) exerts. Participants were advised to report any discomfort, ache or feeling unwell at any point during testing and they were asked to do so every time the pressure settings changed. None of the participants complained of any of these symptoms at any point during testing. In contrary, they found the experience rather pleasant reminding them of massage.

The testing protocol is depicted in Table 3.8

Table 3.8: Testing protocol with the order of testing and data collection document. Every participant was tested three times for each set of pressures on a still, standing up body position.

Testing Protocol									
Position	Cuffs	Cuff Pressure (mmHg)	Individual cuff inflation time (sec)	Deflation time (sec)	Testing time (min)	Velocity Time Integral (VTI) (Stroke Distance) values per cycle (au - arbitrary units)	Mean VTI (au)	Demographics	
Standing	Calf Ankle Foot	40 60 80	5 10 15	30	6	1. 2. 3. 4. 5. 6.		Date & Time	Gender
								/ /	M ☐
				20	5	1. 2. 3. 4. 5. 6.		:	F ☐
								Initials	Age
				10	5	1. 2. 3. 4. 5. 6.			
								Leg	Height
	Calf Ankle Foot	60 80 100	5 10 15	30	6	1. 2. 3. 4. 5. 6.		Right ☐	
				20	5	1. 2. 3. 4. 5. 6.		Left ☐	cm
								Prototype size	Weight
				10	5	1. 2. 3. 4. 5. 6.		L M S	Kg
								Comments	
	Calf Ankle Foot	80 100 120	5 10 15	30	6	1. 2. 3. 4. 5. 6.			
				20	5	1. 2. 3. 4. 5. 6.			
				10	5	1. 2. 3. 4. 5. 6.			
Total									

All participants' data were stored anonymously in a University portable computer. The hypotheses set (Table 3.8) were used to decide which statistical methods and tools were going to be used.

3.8 Statistical Analysis Plan

All statistical analyses were performed using SPSS software (version 22, IBM North America, New York, NY, USA). The primary outcome, or dependent variable, Stroke Distance (AU) was descriptively summarised (mean and standard deviation) across both independent variables (Cuff Pressure Magnitude and Deflation Time). Normality testing was performed with the Wilks-Shapiro test and further assessed with Q-Q plots (linearity supporting normality).

3.8.2 Power Analysis

This investigation designed and developed an intermittent pneumatic cuff system and to perform a pilot study (n=40 healthy Test Subjects). There was no published literature on Stroke Distance from which to base an apriori power analysis. The intent was to utilise the data resulting from this pilot study to compute an a posteriori power analysis from which future studies could be designed. The required sample was computed for a significance level set to $\alpha \leq 0.05$ and a Power of $1-\beta \geq 0.8$ to protect for type I and type II errors, as explained in the Results Section for the a posteriori Power analysis.

3.8.3 Hypothesis 1 Testing

Hypothesis 1 examines the relationship between cuff Pressure (mmHg) and Stroke Distance (AU) while examining for data saturation and the effect of sex and age. To test H1A (Mean Stroke Distance will increase with IPC cuff pressures for each deflation time), a linear regression analysis was performed with Stroke Distance as the dependent variable and cuff Pressure (mmHg) as the independent variable. The p-value was reported to determine if the relationship was significant ($p<0.05$). The correlation coefficient (R) was computed to assess the goodness of fit. The equation of the relationship with corresponding p and R values was computed for the data corresponding to each deflation time (10 sec, 20 sec, and 30 sec). H1A will be accepted if $p<0.05$ for the linear regression and $R>0.5$.

To test H1B (Mean Stroke Distance will saturate for compression pressures beyond 80mmHg.), the Mean Stroke Distance will be computed for 80mmHg and 100mmHg pressure levels. The percent difference will be computed according to the following formula;

% Change in Mean Stroke Distance =

$(\text{Mean Stroke Distance}_{80mmHg} – \text{Mean Stroke Distance}_{100mmHg})/ \text{Mean Stroke Distance}_{80mmHg}$

H1B will be accepted if the Change in Mean Stroke Distance is <5%.

To test H1C (Mean Stroke Distance across IPC pressures will not be significantly different between male and female participants), an analysis of covariance (ANCOVA) will be formed. Mean Stoke Distance will be the dependent variable, Sex and Cuff Pressures will be independent variables, and height and weight will be co-variates. H1C will be accepted if there is no significant difference in mean Stroke Distance between males and females accounting for weight and height.

To test H1D (Mean Stroke Distance across IPC pressures will not be affected by the participants' age), an ANCOVA will be formed. Mean Stoke Distance will be the dependent variable, Age (those above the median age of 39 vs. those below) and Cuff Pressures will be independent variables, and height and weight will be co-variates. H1D will be accepted if there is no significant difference in mean stroke distance between younger and older participants accounting for weight and height.

3.8.4 Hypothesis 2 Testing

Hypothesis 2 examines the relationship between cuff Deflation Time (s) and Stroke Distance (AU) while examining for data saturation and the effect of sex and age. To test H2A (Mean Stroke Distance will increase with increasing deflation time intervals between subsequent IPC compression cycles), a linear regression analysis was performed with Stroke Distance as the dependent variable and Deflation Time (s) as the independent variable. The p-value was reported to determine if the relationship was significant ($p<0.05$). The correlation coefficient (R) was computed to assess the goodness of fit. The equation of the relationship with corresponding p and R values was computed for the data corresponding to each cuff Pressure (60, 80, and 100mmHg). H2A will be accepted if $p<0.05$ for the linear regression and $R>0.5$.

To test H2B (Mean Stroke Distance will saturate below 20 second deflation time intervals between IPC subsequent cycles), the Mean Stroke Distance will be computed for 20 seconds and 10 second deflation times. The percent difference will be computed according to the following formula;

% Change in Deflation Time =

(Deflation $Time_{20sec}$ – Deflation $Time_{10sec}$)/ Deflation $Time_{20sec}$

H2B will be accepted if the Change in Deflation Time is <5%.

To test H2C (Mean Stroke Distance across deflation time intervals will not be significantly different between male and female participants), an analysis of covariance (ANCOVA) will be formed. Mean Stoke Distance will be the dependent variable, Sex and Deflation Times will be independent variables, and height and weight will be co-variates. H2C will be accepted if there is no significant difference in mean stroke distance between males and females accounting for weight and height.

To test H2D (Mean Stroke Distance across time intervals between IPC subsequent cycles will not be affected by the participants' age), an ANCOVA will be formed. Mean Stoke Distance will be the dependent variable, Age (those above the median age of 39 years vs. those below) and Cuff Pressures will be independent variables, and height and weight will be co-variates. H2D will be accepted if there is no significant difference in mean stroke distance between younger and older participants accounting for weight and height.

Chapter 4 – Results

Forty healthy participants met inclusion and exclusion criteria and signed informed consent to participate in this study (20 females, 20 males). The cohort had a mean age of 38.6 years, a mean weight of 74.8 kg and a mean height of 172.8 cm (Table 4.1).

Table 4.1: List of Participants with Demographic Data

Participant	Gender	Age	Weight Kg	Height cm
1	F	39	54	161
2	F	41	70	170
3	F	43	65	167
4	F	60	82	160
5	F	27	53	159
6	F	29	60	164
7	F	35	66	169
8	F	37	78	167
9	F	25	67	172
10	F	29	81	163
11	F	39	68	170
12	F	53	89	171
13	F	41	52	163
14	F	40	55	164
15	F	37	59	168
16	F	29	68	177
17	F	33	59	172
18	F	35	66	162
19	F	60	68	165
20	F	40	60	164
21	M	28	80	171
22	M	39	84	183
23	M	25	83	188
24	M	49	98	187
25	M	52	87	190
26	M	50	71	170
27	M	26	75	178
28	M	24	73	175
29	M	24	76	172
30	M	47	96	183
31	M	44	88	180
32	M	41	82	179
33	M	36	81	184
34	M	57	97	180
35	M	40	88	174
36	M	53	75	175
37	M	29	76	172
38	M	39	81	177
39	M	33	94	188
40	M	37	88	179

4.1 Hypothesis H1A

To test Hypothesis 1A, a linear regression technique was employed, where the dependent variable was Stroke Distance and the independent variable was the mean compression pressures. All data collected were analysed, using the SPSS Statistics software. Three separate analyses were performed, one for each deflation time (time between the combined synchronous deflation of all the cuffs and the next inflation of the distal cuff).

4.1.1 H1A: 10-Second Deflation Time

The first dataset to be analysed was for the 10-second deflation time. Regression analysis demonstrated a linear relationship between compression pressures and mean stroke distance (Figure 4.1). The regression equation was y= -2.4E2+8.11x and R= 0.620.

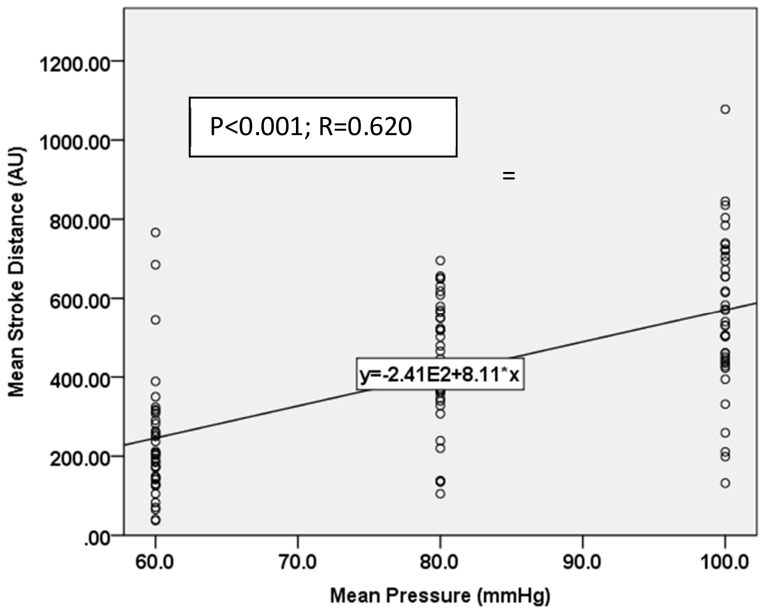


Figure 4.1: Stroke Distance (au) versus Mean Cuff Pressure (mmHg) – 10 second Cuff Deflation Time.

The mean Stroke Distance values for each group of pressures were: 232.93 AU (SD 153.01) for the 60mmHg group, 433.80AU (SD 156.73) for the 80 mmHg group and 557.18AU (SD 193.48) for the 100 mmHg group.

The magnitude of increase between the 60 and 80mmHg groups was 86.24%% and between the 80 and 100mmHg groups was 28.44%.

4.1.2 H1A: 20-Second Deflation Time

The second regression analysis was for the 20-second deflation time. Figure 4.2 shows a positive relationship between mean pressures and stroke distance was observed (R= 0.629).

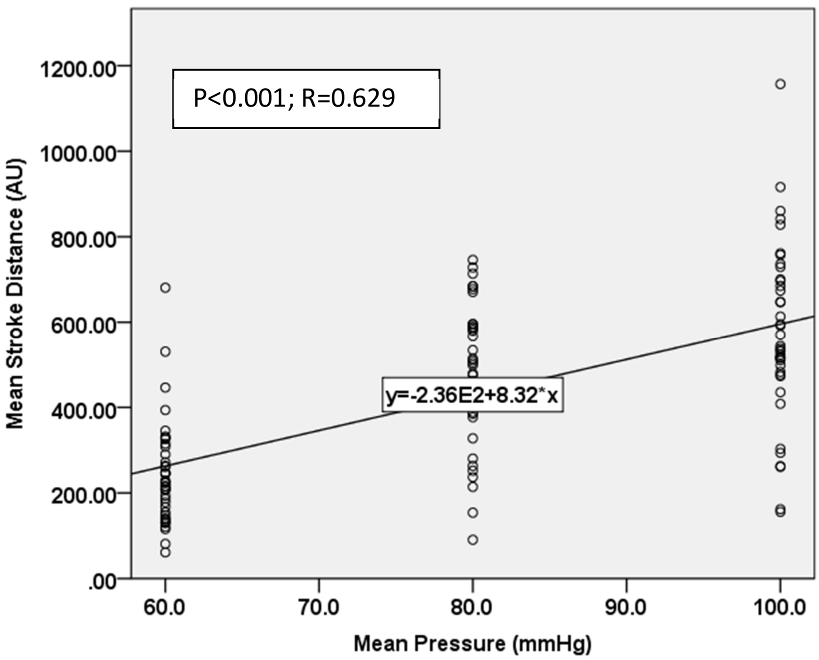
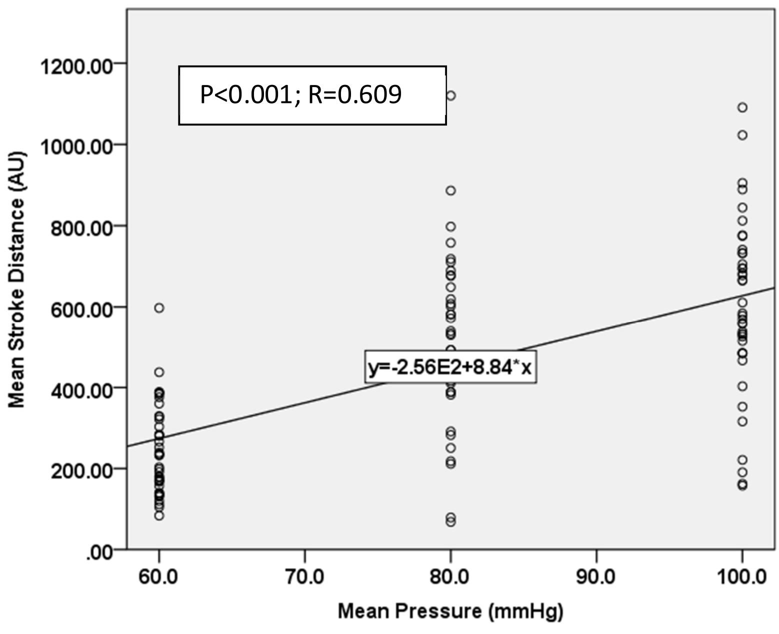


Figure 4.2: Mean Total Stroke Distance (AU) versus Mean Pressure (mmHg) – 20-Second Cuff Deflation Time

The mean Stroke Distance for the 60mmHg group was 241.16 AU (SD 121.08), for the 80mmHg group 472.90 AU (SD 162.52) and for the 100mmHg it was 573.78 AU (SD 206.01). The magnitude of increase between the 60 and 80mmHg groups was 96.09% and between the 80 and 100mmHg groups was 21%.

4.1.3 H1A: 30-Second Deflation Time

The third regression analysis was for the 30-second deflation time (Figure 4.3). A positive relationship was observed between mean pressure and mean stroke distance with an R-value of 0.609.



Regression

Figure 4.3: Stroke Distance (AU) versus Mean Pressure (mmHg) – 30-second Cuff Deflation Time

The mean Stroke Distance for the 60mmHg group was 244.87 AU (SD 111.53), for the 80mmHg group 509.29 AU (SD 209.30) and for the 100mmHg it was 598.34 AU (SD 216.95). The magnitude of increase between the 60 and 80mmHg groups was 107.98% and between the 80 and 100mmHg groups was 17.49%.

All three deflation time regression analyses demonstrated strong positive relationships between stroke distance and mean pressure. These relationships were significant and had similar correlation coefficients. Hypothesis H1A is therefore accepted.

It was also found that the percent increase in stroke distance, for the different deflation times, from average cuff pressure of 60 mmHg to 80 mmg was three to six times higher than those between 80 mmHg and 100mmHg.

4.2 Hypothesis H1B

The mean stroke distance was hypothesised to saturate for compression pressures beyond 80 mmHg. In other words, the haemodynamic effects of external pneumatic compression would stop improving significantly beyond a certain pressure level. In this case, the level of mean pressure was set at 80 mmHg. This hypothesis would be accepted if the stroke distance was <5% different at 100mm/Hg, compared to 80 mm/Hg.

Table 4.1.1: Statistics of the Stroke Distance readings for the groups of 80 mmHg (left) and 100 mmHg (right) mean cuff pressures

Mean Cuff Pressure 80mmHg

N	Valid	
	Missing	
Mean		
Median		
Std. Deviation		
Range		
Minimum		
Maximum		

Mean Cuff Pressure 100mmHg

Mean Stroke Distance (AU)

N	Valid	120
	Missing	0
Mean		576.40
Median		564.00
Std. Deviation		204.662
Range		1025
Minimum		132
Maximum		1157

The mean stroke distance was calculated for the two pressure levels (80 mmHg and 100 mmHg) and the percentage difference was calculated. The mean stroke distance for the mean 80 mmH pressure was 471.97 AU, whereas the mean stroke distance for 100 mmHg was 576.40 AU. The difference in stroke distance was 104.42 AU, an 18.12% increase. This hypothesis was therefore rejected as the stroke distance did not saturate at 80 mmHg.

4.3 Hypothesis H1C

It was hypothesised that the mean stroke distance across the tested IPC pressure levels (60, 80, and 100 mmHg) would not be significantly different between male and female participants. This hypothesis would be accepted if there was no significant difference in ANCOVA for the mean Stroke Distance between males and females, accounting for weight and height.

The analysis of covariance (ANCOVA) demonstrated that mean stroke distance for the same compression pressures did not differ between genders (Table 4.2). There was no significant difference (p=0.877) in stroke distance across IPC pressures between male and female participants.

Table 4.2: ANCOVA Mean Stroke Distance across Deflation Time – Effect of Gender

Mean Pressure (mmHg)	Gender	Mean	SD	p Value Gender
60	Female	227.82	127.24	0.877
	Male	251.5	130.26	
80	Female	445.16	201.9	
	Male	498.84	149.53	
100	Female	524.18	230.47	
	Male	628.7	160.7	
Total	Female	399.1	228.19	
	Male	459.68	214.69	

4.4 Hypothesis H1D

It was hypothesised that mean stroke distance across mean pressures would not be affected by the participants' age. This hypothesis would be accepted if there was no significant difference in ANCOVA between those participants above the median age and those below the median age, accounting for weight and height. The participants were stratified into two groups, based on the median age of 39 years. The younger group had 19 participants and the older group had 21 participants. Analysis of co-variance was performed.

The results show no significant difference in Stroke Distance across mean pressures (p = 0.492) between the two age groups, accounting for height and weight (Table 4.3).

Table 4.3: ANCOVA Mean Stroke Distance across Deflation Time – Effect of Age

Mean Pressure (mmHg)	Age Category	Mean	SD	p Value Age
60	Younger	214.07	96.57	0.492
	Older	262.79	149.11	
80	Younger	461.46	180.47	
	Older	481.49	178.48	
100	Younger	588.12	229.47	
	Older	565.79	180.54	
Total	Younger	421.22	235.41	
	Older	436.70	212.10	

4.5 Hypothesis H2A

It was hypothesised that mean stroke distance would increase with increasing deflation time intervals between subsequent IPC compression cycles for each cuff pressure. To test the Hypothesis 2A, a linear regression analysis was employed, where the dependent variable was Stroke Distance and the independent variable was the deflation times. Three separate analyses were performed, one for each mean cuff pressure.

Note*: There is a maximum deflation time interval = 30 sec. It is anticipated that allowing more time between cuff compression (ie using longer deflation times), would allow the foot and calf veins to fill with more blood. Ergo, with longer deflation times we should expect higher stroke distance for the same compression pressures. In this case the relationship stroke distance – deflation time was assessed separately for the three different mean compression pressure values.

4.5.1 H2A: 60-mm Hg Cuff Pressure

Regression analysis for the 60-mm Hg cuff pressure demonstrated no relation between mean stroke distance and deflation times (p = 0.679) (Figure 4.4).

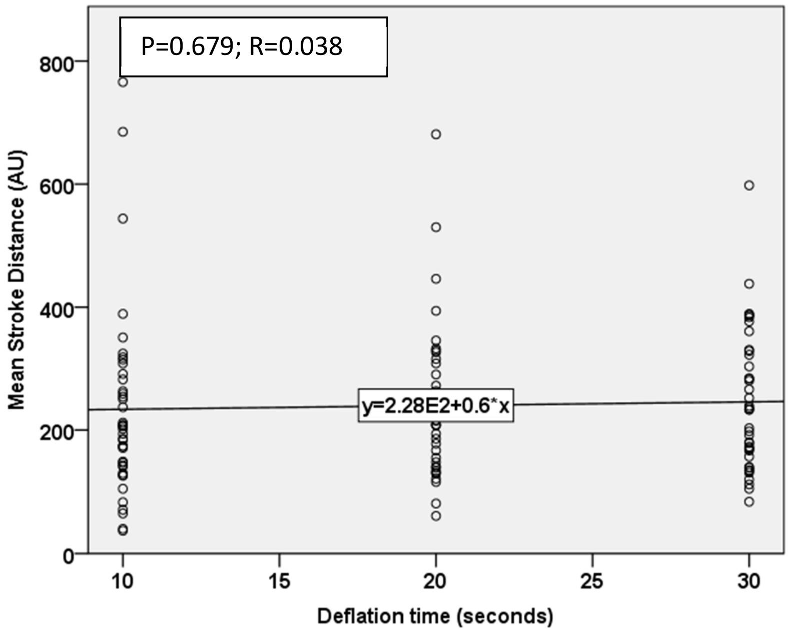


Figure 4.4: Stroke Distance (AU) versus Deflation Time (s) – 60mmHg Cuff Pressure

4.5.2 H2B: 80-mm Hg Cuff Pressure

Regression analysis for the 80-mm Hg cuff pressure demonstrated no relation between mean stroke distance and deflation times (p = 0.059) (Figure 4.5).

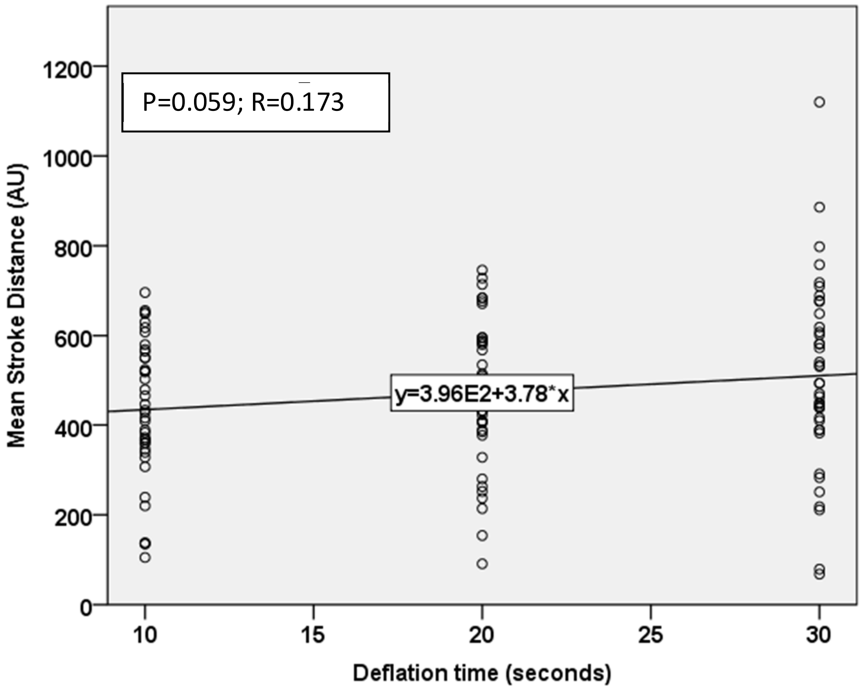


Figure 4.5: Stroke Distance (au) versus Deflation Time (s) – 80mmHg Cuff Pressure

4.5.3 H2B: 100-mm Hg Cuff Pressure

Regression analysis for the 100-mm Hg cuff pressure demonstrated no relation between mean stroke distance and deflation times (p = 0.371) (Figure 4.6).

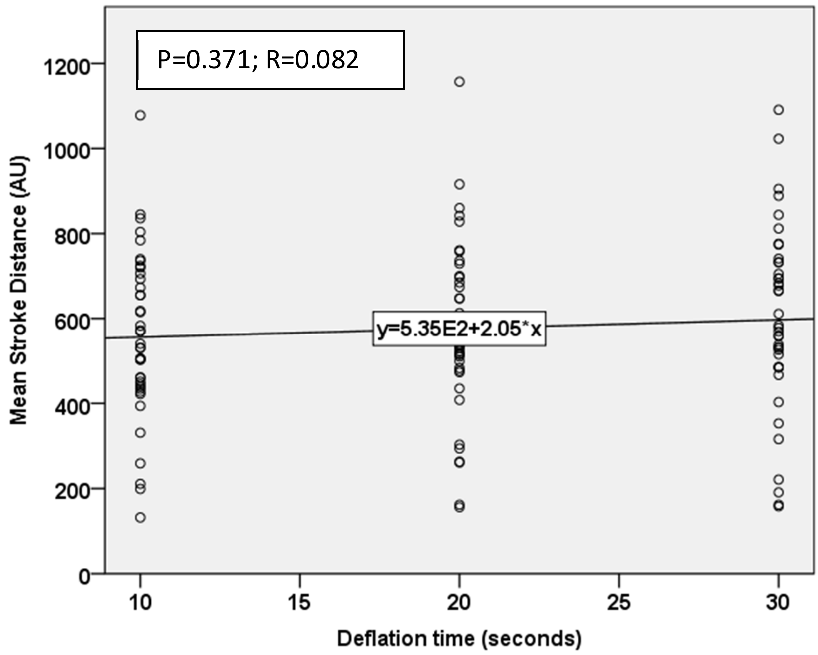


Figure 2c: Stroke Distance (au) versus Deflation Time (s) – 100mmHg Cuff Pressure

None of the separately assessed models for different IPC pressures showed a significant relationship between stroke distance and deflation times. Deflation times of 10, 20 and 30 seconds did not affect stroke distance, irrespective of the set of IPC pressures used.

4.7 Hypothesis H2B

The mean stroke distance was hypothesised to saturate below 20-second deflation times between subsequent IPC cycles. In other words, the haemodynamic effects of external pneumatic compression will stop improving significantly below a certain deflation time. This hypothesis would be accepted if stroke distance was < 5% different at for deflation time of 20 s compared to that at 10s.

Mean stroke distance was calculated for the two deflation times (20 s and 10 s) and the percentage difference was calculated. Mean stroke distance for the 20-s deflation time was 429 AU, whereas the mean stroke distance for the 10-s deflation time was 407 AU. The difference between them was 22 AU, a 5.12% increase, which was above the set 5% rejection criteria. This hypothesis is therefore rejected as the stroke distance did not saturate at 20 s.

4.8 Hypothesis H2C

It was hypothesised that mean stroke distance across deflation times (10sec, 20sec, 30sec) would not be affected by the participants' gender. This hypothesis would be accepted if there was no significant difference in ANCOVA between male and female participants, accounting for weight and height.

The results showed no significant difference (p=0.907) in stroke distance across deflation time between males and females, accounting for height and weight (Table 4.7). Hence, participants' gender did not affect the relationship between compression pressures and stroke distance.

Table 4.7: ANCOVA Mean Stroke Distance Across Deflation T – Effect of Gender

Deflation Time (sec)	Gender	Mean	Std	p Value Gender
10	Female	376.90	222.60	0.907
	Male	439.04	203.14	
20	Female	399.37	223.78	
	Male	459.19	206.76	
30	Female	420.88	239.52	
	Male	480.80	234.37	
Total	Female	399.05	228.19	
	Male	459.68	214.69	

4.9 Hypothesis H2D

It was hypothesised that mean stroke distance across deflation times would not be affected by the participants' age. This hypothesis would be accepted if there was no significant difference in ANCOVA between those participants above the median age and those below the median age, accounting for weight and height.

The results showed no significant difference (p=0.603) in stroke distance across deflation time between the two age groups, accounting for height and weight (Table 4.8).

Table 4.8: ANCOVA Mean Stroke Distance across Deflation Time -Effect of Age

Deflation Time (s)	Age Category	Mean	Std	p Value Age
10	Younger	401.91	232.46	0.603
	Older	413.44	198.59	
20	Younger	422.16	232.77	
	Older	435.63	202.51	
30	Younger	439.58	243.49	
	Older	461.00	234.08	
Total	Younger	421.22	235.41	
	Older	436.70	212.10	

Chapter 5 – Discussion

5.1 Summary of major findings

Pneumatic compression is an established method of improving the venous flow of the lower limbs. It is used as a treatment method for patients with complicated venous disease and as prophylaxis for deep venous thrombosis. Other indications include lymphoedema, end stage arterial disease, and sports recovery. As technology improves, the size of Intermittent Pneumatic Compression (IPC) devices decreases making them more user-friendly and popular. Their effects upon human physiology is multi-dimensional, including flow enhancement, reduction of oedema and release of anticoagulation factors. Although their use steadily increases the optimal parameter settings for IPC devices remain an area of current research.

The prototype IPC device designed and developed in this research employed three inflatable cuffs (foot, ankle, and calf) with sequential compression from distal to proximal. The IPC boot was under real-time control from a smartphone based App that provided adjustable compression pressure magnitudes and cuff deflation times. This permitted varying the length of a compression cycle, the length of the deflation period, duration of cuff compression, and the time to achieve target cuff pressure.

Upon IPC prototype evaluation of forty healthy volunteers a significant positive relationship between mean stroke distance and cuff pressure magnitude was observed for 10 seconds ($p<0.001$, $R=0.620$), 20 seconds ($p<0.001$, $R=0.629$), and 30 seconds ($p<0.001$, $R=0.609$) deflation times. Mean Stroke Distance did not saturate at 80mm Hg and was not affected by sex or age across deflation times. Mean Stroke Distance was not significantly related to deflation times, irrespective of the magnitude of applied cuff pressure. Mean Stroke Distance did not saturate below 20 second deflation times. Mean Stroke Distance across pressure levels was not affected by sex or age. The main determinant of haemodynamic effects was the magnitude of cuff compression pressure irrespective of gender or age.

5.2 Theoretical and Clinical Factors

The vast majority of the IPC devices are used for prophylaxis from Deep Venous Thrombosis (DVT). The second major indication is the treatment of venous ulcers. The common pathophysiologic ground in both conditions is stagnation (stasis) of blood in the leg veins. According to Virchow (1859), the combination of venous stasis, damaged venous endothelium and blood hypercoagulability is the main cause of DVT. Long-term venous stasis is the main cause of venous hypertension that leads to venous ulceration. Venous stasis is, therefore, the common denominator that requires particular attention when intending to use a PC device.

Also important as an outcome of PC action is the enhancement of fibrinolytic activity that acts as a protector from the formation of thrombi in the veins. This latter effect is not examined in this research but there is enough evidence in the literature to support it.

The three-cuff prototype design is based on physiological observations of the foot and calf musculo-venous pumps that assist the heart with venous return during walking. Preliminary testing indicated that all three cuffs contribute to venous return. When the foot cuff was not used, the Stroke Distance was lower for the same target pressures of the remaining two cuffs. It appears that the foot cuff compression provides an initial boost to venous return from which a momentum is built for the proximal cuffs to create a more significant haemodynamic effect.

Kamm (1979, 1982), demonstrated the superiority of sequential, graded, asymmetric compression. It is widely accepted that the venous pressure at the level of the ankle on a standing up adult of average height is around 90 mmHg (Guyton, 2015). The lowest set of pressures chosen to test was 80/60/40 mmHg for the foot, ankle, and calf cuff target pressures.

Nicolaides (1980) used Doppler velocimetry to compare the haemodynamic (velocity) effects of two IPC devices a single-chambered and a six-chambered one. It was demonstrated that the multi-chambered device was more effective in increasing the venous blood velocity. They tried five different set of pressures over a fixed cycle of 12 seconds of compression and 60 seconds of deflation and they found that the set of pressures to cause the optimal effect on femoral vein velocity in the supine position was 35, 30 and 20 mmHg for the ankle, the calf and the thigh cuffs respectively. Kamm (1986) experimented on the optimal variation from cuff to cuff on multi-chamber IPCC devices and concluded that the optimal graded and sequential pattern was at the values of 5-10 mmHg differences the highest being more distally).

Muhe (1984) experimented on increasing compression pressures over 55 mmHg and studied changes in velocity on subjects on semi-recumbent position. He used an IPC device with 20% pressure increments from cuff to cuff and observed 175% increase with a mean pressure of 35 mmHg, 304% for 65 mmHg, and 366% for 95 mmHg. His conclusion was that the norm at the time 55 mmHg was too low to produce high velocities.

Pekanmaki (1987) experimented with 50 mmHg and mild pressure gradients (15 mmHg). They studied mostly clinical outcomes and succeeded treating ulcers with that pressure, an inflation time of 12 seconds and a frequency of 2 compression cycles per minute, which allowed an 18 seconds deflation (or rest) period between cycles.

Whitelaw (2001) assessed the ability of six IPC devices to increase femoral venous blood flow velocity and compared it to that of active and passive foot dorsiflexion. The participants were placed supine with the head of the bed elevated 30^0 to the horizontal in a recumbent position. They found that the device with multiple cuffs and higher pressure settings compared to the other devices was the only one to simulate best foot dorsiflexion Figure 5.1. Their similarities in pressure waveform in Whitelaw's study and those in this study (Figure 3.27) are to be noted.

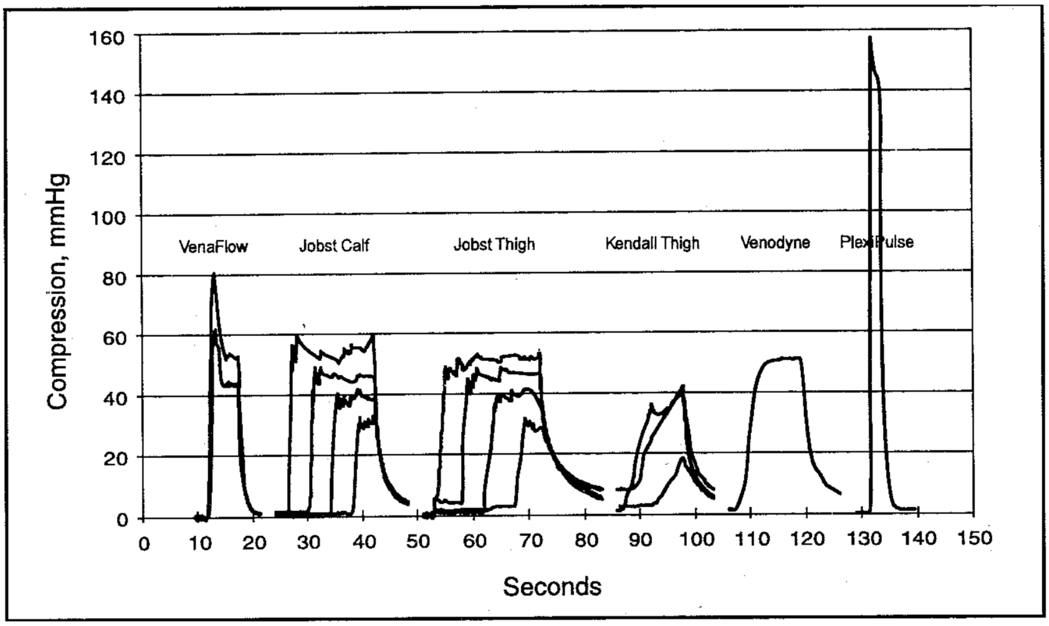


Figure 5.1: Comparison of six IPC devices. Compression pressures over time. Pressure levels variation and individual cuff inflation times. Adapted from Whitelaw, G.P. et al., 2001. Evaluation of intermittent pneumatic compression devices. Orthopaedics, 24(3), pp.257–261

The current gold standard method for the assessment of blood flow through a blood vessel is considered to be the duplex ultrasound. In this technique, the vessel is visualised and its diameter is measured followed by measurement of the blood velocity. The product of diameter times velocity is flow, which is a widely accepted index of circulation. This measurement is quite accurate for arteries which have non-compliant walls with a dominant muscular element and a fixed diameter, even when the intravascular pressure drops or increases dramatically. Veins, however, responsible for storing blood, that is used when needed, have a much higher compliance and their diameters change quickly and frequently with changes of the intravascular and extraluminal pressures.

Katz (1969), in the pre-duplex ultrasound era, acknowledging the problem of assessing the flow in a collapsible tube (such as veins and lung bronchi) experimented in developing a mathematical model to predict their behaviour. Carpenter (2003) highlighted the complexity of describing flow in collapsible tubes and particularly emphasised the challenge that self-excited oscillations introduce to this matter. They recommended a combined theoretical, computational and experimental approach to the problem. The above highlight that the flow in a highly compliant vessel such as a vein is difficult to measure.

Another way of assessing venous flow in the lower limb is plethysmography which can accurately trace and quantify changes of the volume of the leg either using invasive methods (strain gauge – needle - plethysmography) or by using light emission (photoplethysmography) or pneumatic cuffs (air plethysmography). Apart from invasive (strain gauge) these methods can be slow and time-consuming and/or impractical and complex.

Stroke Distance, a well-documented index used in echocardiography, was used extensively in this research as the main indicator of changes in the lower limb venous haemodynamics during application of Intermittent Pneumatic Compression. Its measurement does not require knowledge of the vessel diameter (e.g. aorta), which makes it particularly useful when the vessel cannot be adequately visualised or its diameter is subjected to continuous change. The human thoracic aorta is a very difficult vessel to visualize with ultrasound because of its position within the rib cage. Veins, on the other hand, are very compliant and their size varies dramatically depending upon the amount of blood they contain and the external pressure from the surrounding tissues.

Goldman (2000) researched the correlation of the Left Ventricular Output Stroke Distance on patients with heart disease and found good correlation with established indices of cardiac function. Trent 1999 reported that Stroke Distance was the strongest independent predictor of survival among patients with myocardial infarction.

Firstenberg (2000) explained that Stroke Distance reflects physiologically the work of the heart against its afterload which is a better index of the cardiac function that its ejection fraction. In analogy, the musculo-venous pump of the calf is a peripheral pumping mechanism and, as such, the same assessment of function can be applied.

Muhe (1984) experimented on increasing compression pressures over 55 mmHg and studied changes in velocity. He used an IPC device with 20% pressure increments from cuff to cuff and observed 175% increase with a mean pressure of 35 mmHg, 304% for 65 mmHg, and 366% for 95 mmHg. His conclusion was that the norm at the time 55 mmHg was too low to produce high velocities.

The hypotheses were posed to investigate the physiologic haemodynamic consequences of intermittent pneumatic compression to assess: (1) the relationship between compression pressure and flow changes and (2) the relationship between compression frequency and flow change. The sets of pressures used (80/60/40 mmHg, 100/80/60 mmHg and 120/100/80 mmHg) had a significant positive relationship with flow enhancement and there were no signs of saturation at their maximum pressure. Compared with the literature in a research setting, Delis (2000) experimented with an array of compression pressures ranging from 60 to 140 mmHg measuring directly the venous pressure (pressure transducer connected to a vein in the foot). They used sequential intermittent pneumatic compression devices originally designed to treat arterial disease. They observed that the higher the set of compression pressures the more significant the drop of venous pressure

In a clinical setting, current manufactured technology for IPC is employing a similar range of cuff pressures. However, the functional parameters cannot be fully controlled. Advantages inherent in the new design are its versatility, the full control over its functional parameters, its portability and the possibility of developing personalised treatments that are optimised for each patient's disease or risk factors.

Higher pressures could potentially further increase blood flow. Although encouraging, it still remains to be determined what the safe upper bound pressure for IPC would be. Also of practical value would be to determine the minimum effective set of compression pressures in a patient cohort.

The data did not support a relationship between pressure magnitude and cuff deflation times (10, 20 and 30 seconds). It is possible that deflation times used were not long enough for the veins to refill in healthy individuals. Still, however, refilling of the veins happens continuously and gradually and partial refilling should be expected, especially for the 30 seconds deflation time value. Nicolaides (1980) considered a deflation time of at least 45 seconds to be crucial, but they did all their testing on participants who were either lying down or were in semi-recumbent position.

Individuals with venous insufficiency are likely to have completely different results. From the treatment perspective, future research should determine the maximum deflation time that produces the largest haemodynamic response. Long deflation times make compression less uncomfortable and more energy efficient. In the case of the tested participants, since deflation times up to 30 seconds did not affect the haemodynamic outcome, the maximum deflation time should be used. This may not be the case for patients with venous insufficiency, as their venous refilling times are significantly shorter.

Gender and age did not affect stroke distance in this healthy population. If this finding holds for the venous insufficiency population then it would simplify the use of IPC technology because the data would not require adjustment. These results would need confirmation on populations with venous disease before making this assumption though.

This study was limited to healthy individuals as it is introducing a novel way of measuring the haemodynamic effects of IPC. After proof of concept, gait analysis, and reliability tests, this was considered to be the next logical step. One of the reasons the device was designed and built in the University is that it will continue to be serving the purpose of further research. Indeed, there is broad room for experimentation using different combinations of settings but most importantly different body positions. The choice of the upright position for the needs of this study was deliberate as it allows easier exposure and access to the popliteal fossa. This gave us the opportunity to gain experience with the technique of probe placement and made it possible for the flow to be checked by using other methods at the same time.

5.3 Strengths and Limitations of the Research

5.3.1 Limitations

Stroke Distance (the velocity-time integral) represents distance travelled by blood flow. In this research, the signal acquired by the Doppler device was not quantified in terms of velocity. The aim was to explore the relationship of external compression and changes in venous haemodynamics and not to measure absolute velocity. Therefore, the use of an arbitrary unit was justified. Furthermore, Stroke Distance is an accurate means to compare the percentage of change in a single individual from measurement to measurement but it would not make a reliable tool to compare haemodynamic differences across multiple individuals.

The positioning of the Doppler probe is an important procedure since only slight changes in position can alter the Doppler output signal. This is true not only for the anatomical positioning of the probe but also for the angle of the emission and reception of the Doppler To minimise position errors, a standard method of tracing the popliteal artery signal first and placing the probe just laterally to it was employed. The mechanism of attaching the probe to the chosen location proved to be reliable and did not allow displacement during testing with the participant standing still. All participants were healthy individuals with no history or active venous disease. Patients with venous disease would be likely to have different haemodynamics in response to Pneumatic Compression.

Another limitation is that the Stroke Distance is not a true integration of the Continuous Wave (CW) Doppler.

There are numerous possible combinations of cuff pumping parameters for an IPC device. This research examined only a limited number of these parameters for practical reasons. The parameters selected in this research, however, were based upon the existing literature describing venous physiology, anatomy and fluid engineering.

5.3.2 Strengths

A novel intermittent pneumatic compression device with a comprehensive set of adjustable controls was designed, built and tested for reliable and safe use to enhance stroke distance. The study introduces a novel practical, reliable and real-time parameter (Stroke distance) for testing the effects of IPC on haemodynamics effect.

Data was collected in a manner which did not require a sonographer, making this device very useful as a research tool. The prototype IPC boot has a built-in feedback mechanism in the sense that a desirable stroke distance can be set and the software may alter the compression settings (cuff pressures and inflation/idle times) in order to meet set target stroke distance values. Note: this feature was not tested or used in the present research.

5.3.3 Future work

The next step would be to test patients with complicated chronic venous insufficiency (venous ulcers) and/or use the device as prophylaxis for Deep Venous Thrombosis (DVT) which currently are the main indications IPC use.

The novel IPC device that was developed also has a feedback mode option which was not used in the current research. It is important that further testing be performed and data collected and analysed to help us further our understanding of IPC triggered venous haemodynamic enhancement.

Chapter 6 – Conclusion

6.1 Conclusions

IPC technology is currently an adjuvant to compression bandaging for venous ulcers and pharmacologic prophylaxis from Deep Venous Thrombosis. Although it has been introduced decades ago, the advances in technology only recently allowed it to become more user-friendly by reducing its size and making possible portable versions.

IPC devices can vary greatly in terms of physical characteristics and function settings – the number of combinations of pressure magnitude and timing variables can be perplexing. Existing literature provides a relatively narrow range of variable values with a paucity of objective data. This in part is due to the technical difficulty in obtaining real-time, continuous measurements with existing techniques in different body positions. A glaring example is a sitting subject. This is the commonest body position for elderly people with poor mobility, inefficient calf muscle pump, and venous ulceration. Conventional venous ultrasound of the popliteal or the femoral vein is extremely difficult to perform on a seated subject.

This dissertation introduces a novel way of assessing the haemodynamic effects of IPC that is continuous, safe and performed in real time. Stroke Distance is a promising index of flow change and can be potentially utilised more widely in the field of haemodynamics.

Gait analysis suggests that the device could be used while standing or walking without substantially affecting one's natural movement. There were no adverse events during testing, supporting the safety of this non-invasive technology. Further testing showed that, although sometimes silent to Doppler, all three cuffs contribute to the final haemodynamic effect. A possible explanation is that foot compression has a priming effect on the calf veins by filling them with propelled volume of blood from below.

The analysis of data collected from forty healthy subjects showed that there is a positive relationship between compression pressures and Stroke Distance at least for the pressure and time parameters used.

The lack of an effect for age and sex upon stroke distance and deflation times potentially simplifies the application of IPC. Deflation times were not related to Stroke Distance. One explanation might be that the study participants were healthy and the deflation times relatively short for non-refluxing veins.

Appendix

Proximal pressure											For mean				For Bland Altman plot			
Group	Pressure_combinatio	Label	Symbol	Cofactor	Sample_size	Mean	Variance	SD	CV_pct	**Standard_error**	**Lower_CI**	**Upper_CI**	Length	Length_pct	**Approx_Lower_C**	**Approx_Upper_C**	Approx_Length	Approx_Length_pc
1	A	80-60-40	A	Sitting	10	4999.5	179582.1	423.8	8.5	134.0	4696.4	5302.7	606.3	12.1	4736.9	5262.2	525.3	10.5
2	B	100-80-60	B	Sitting	10	5869.3	145076.6	380.9	6.5	120.4	5596.8	6141.8	544.9	9.3	5633.2	6105.4	472.2	8.0
3	C	110-90-70	C	Sitting	10	6604.1	195476.8	442.1	6.7	139.8	6287.9	6920.4	632.6	9.6	6330.1	6878.2	548.1	8.3
4	D	120-100-80	D	Sitting	10	7376.2	303498.9	550.9	7.5	174.2	6982.1	7770.3	788.2	10.7	7034.7	7717.7	682.9	9.3
5	E	140-120-10	E	Sitting	10	8377.1	3735.3	61.1	0.7	19.3	8333.4	8420.9	87.4	1.0	8339.3	8415.0	75.8	0.9
6	F	150-130-11	F	Sitting	10	9083.9	1424.1	37.7	0.4	11.9	9056.9	9110.9	54.0	0.6	9060.6	9107.3	46.8	0.5
7	G	80-60-40	G	Standing	10	5144.7	170869.6	413.4	8.0	130.7	4849.0	5440.4	591.4	11.5	4888.5	5400.9	512.4	10.0
8	H	100-80-60	H	Standing	10	5890.8	163098.4	403.9	6.9	127.7	5601.9	6179.7	577.8	9.8	5640.5	6141.1	500.6	8.5
9	I	110-90-70	I	Standing	10	6506.7	210790.2	459.1	7.1	145.2	6178.3	6835.2	656.9	10.1	6222.2	6791.3	569.1	8.7
10	J	120-100-80	J	Standing	10	7229.4	295149.8	543.3	7.5	171.8	6840.7	7618.0	777.3	10.8	6892.6	7566.1	673.5	9.3
11	K	140-120-10	K	Standing	10	8354.3	5904.9	76.8	0.9	24.3	8299.3	8409.2	109.9	1.3	8306.6	8401.9	95.3	1.1
12	L	150-130-11	L	Standing	10	8762.4	447384.5	668.9	7.6	211.5	8284.0	9240.9	957.0	10.9	8347.9	9177.0	829.1	9.5

Intraclass correlation coefficient (and 95% confidence limits) 0.917 0.838 0.970

Repeatability coefficient 1165.6
On 95% of occasions two readings should differ by no more than this.

Middle pressure											For mean				For Bland Altman plot			
Group	Pressure_combinatio	Label	Symbol	Cofactor	Sample_size	Mean	Variance	SD	CV_pct	**Standard_error**	**Lower_CI**	**Upper_CI**	Length	Length_pct	**Approx_Lower_C**	**Approx_Upper_C**	Approx_Length	Approx_Length_pc
1	A	80-60-40	A	Sitting	10	3574.3	187942.1	433.5	12.1	137.1	3264.1	3884.4	620.2	17.4	3305.6	3843.0	537.4	15.0
2	B	100-80-60	B	Sitting	10	4290.4	312079.2	558.6	13.0	176.7	3890.8	4690.1	799.3	18.6	3944.2	4636.7	692.5	16.1
3	C	110-90-70	C	Sitting	10	4827.1	416356.2	645.3	13.4	204.0	4365.6	5288.7	923.2	19.1	4427.2	5227.1	799.9	16.6
4	D	120-100-80	D	Sitting	10	5342.6	569433.2	754.6	14.1	238.6	4802.8	5882.5	1079.6	20.2	4874.9	5810.4	935.4	17.5
5	E	140-120-10	E	Sitting	10	6580.6	27578.8	166.1	2.5	52.5	6461.8	6699.4	237.6	3.6	6477.7	6683.6	205.9	3.1
6	F	150-130-11	F	Sitting	10	7055.1	3047.4	55.2	0.8	17.5	7015.6	7094.5	79.0	1.1	7020.8	7089.3	68.4	1.0
7	G	80-60-40	G	Standing	10	3579.4	198048.7	445.0	12.4	140.7	3261.0	3897.7	636.7	17.8	3303.6	3855.2	551.7	15.4
8	H	100-80-60	H	Standing	10	4335.2	337552.4	581.0	13.4	183.7	3919.6	4750.9	831.2	19.2	3975.1	4695.3	720.2	16.6
9	I	110-90-70	I	Standing	10	4831.0	422247.2	649.8	13.5	205.5	4366.1	5295.8	929.7	19.2	4428.2	5233.7	805.5	16.7
10	J	120-100-80	J	Standing	10	5365.5	576469.8	759.3	14.2	240.1	4822.4	5908.7	1086.3	20.2	4894.9	5836.1	941.2	17.5
11	K	140-120-10	K	Standing	10	6569.4	1512.5	38.9	0.6	12.3	6541.6	6597.2	55.6	0.8	6545.3	6593.5	48.2	0.7
12	L	150-130-11	L	Standing	10	6689.1	943620.0	971.4	14.5	307.2	5994.2	7384.0	1389.8	20.8	6087.0	7291.1	1204.2	18.0

Intraclass correlation coefficient (and 95% confidence limits) 0.816 0.671 0.930

Repeatability coefficient 1599.5
On 95% of occasions two readings should differ by no more than this.

Distal pressure											For mean				For Bland Altman plot			
Group	Pressure_combinatio	Label	Symbol	Cofactor	Sample_size	Mean	Variance	SD	CV_pct	**Standard_error**	**Lower_CI**	**Upper_CI**	Length	Length_pct	**Approx_Lower_C**	**Approx_Upper_C**	Approx_Length	Approx_Length_pc
1	A	80-60-40	A	Sitting	10	2583.8	190335.2	436.3	16.9	138.0	2271.7	2895.8	624.2	24.2	2313.3	2854.2	540.8	20.9
2	B	100-80-60	B	Sitting	10	3116.7	265264.8	515.0	16.5	162.9	2748.3	3485.1	736.9	23.6	2797.5	3435.9	638.4	20.5
3	C	110-90-70	C	Sitting	10	3586.0	324688.6	569.8	15.9	180.2	3178.4	3993.7	815.2	22.7	3232.9	3939.2	706.3	19.7
4	D	120-100-80	D	Sitting	10	3943.3	476015.0	689.9	17.5	218.2	3449.7	4436.8	987.1	25.0	3515.6	4370.9	855.3	21.7
5	E	140-120-10	E	Sitting	10	4962.7	6455.5	80.3	1.6	25.4	4905.2	5020.1	115.0	2.3	4912.9	5012.5	99.6	2.0
6	F	150-130-11	F	Sitting	10	5368.0	2186.6	46.8	0.9	14.8	5334.6	5401.5	66.9	1.2	5339.1	5397.0	58.0	1.1
7	G	80-60-40	G	Standing	10	2534.1	205194.2	453.0	17.9	143.2	2210.0	2858.1	648.1	25.6	2253.3	2814.8	561.5	22.2
8	H	100-80-60	H	Standing	10	3091.7	273623.7	523.1	16.9	165.4	2717.5	3465.8	748.4	24.2	2767.4	3415.9	648.4	21.0
9	I	110-90-70	I	Standing	10	3554.3	361206.2	601.0	16.9	190.1	3124.3	3984.2	859.9	24.2	3181.7	3926.8	745.0	21.0
10	J	120-100-80	J	Standing	10	3978.4	496892.7	704.9	17.7	222.9	3474.2	4482.7	1008.5	25.3	3541.5	4415.3	873.8	22.0
11	K	140-120-10	K	Standing	10	5085.5	126.8	11.3	0.2	3.6	5077.5	5093.6	16.1	0.3	5078.5	5092.5	14.0	0.3
12	L	150-130-11	L	Standing	10	5163.9	806830.1	898.2	17.4	284.0	4521.4	5806.5	1285.1	24.9	4607.2	5720.7	1113.5	21.6

Intraclass correlation coefficient (and 95% confidence limits) 0.780 0.619 0.914

Repeatability coefficient 1477.3
On 95% of occasions two readings should differ by no more than this.

Total pressure											For mean				For Bland Altman plot			
Group	Pressure_combinatio	Label	Symbol	Cofactor	Sample_size	Mean	Variance	SD	CV_pct	**Standard_error**	**Lower_CI**	**Upper_CI**	Length	Length_pct	**Approx_Lower_C**	**Approx_Upper_C**	Approx_Length	Approx_Length_pc
1	A	80-60-40	A	Sitting	10	######	#######	#####	11.5	406.7	10237.4	12077.7	1840.3	16.5	10360.3	11954.8	1594.5	14.3
2	B	100-80-60	B	Sitting	10	######	#######	#####	10.9	458.9	12238.2	14314.6	2076.4	15.6	12376.9	14176.0	1799.1	13.6
3	C	110-90-70	C	Sitting	10	######	#######	#####	11.0	523.0	13834.3	16200.4	2366.1	15.8	13992.3	16042.3	2050.0	13.7
4	D	120-100-80	D	Sitting	10	######	#######	#####	12.0	630.4	15236.1	18088.1	2852.0	17.1	15426.6	17897.7	2471.1	14.8
5	E	140-120-10	E	Sitting	10	######	76308.9	276.2	1.4	87.4	19722.8	20118.1	395.2	2.0	19749.2	20091.7	342.4	1.7
6	F	150-130-11	F	Sitting	10	######	12296.8	110.9	0.5	35.1	21427.7	21586.4	158.7	0.7	21438.3	21575.8	137.5	0.6
7	G	80-60-40	G	Standing	10	######	#######	#####	11.6	413.7	10322.3	12194.0	1871.8	16.6	10447.3	12069.0	1621.7	14.4
8	H	100-80-60	H	Standing	10	######	#######	#####	11.3	475.2	12242.7	14392.7	2150.0	16.1	12386.3	14249.1	1862.8	14.0
9	I	110-90-70	I	Standing	10	######	#######	#####	11.5	539.9	13670.6	16113.3	2442.6	16.4	13833.8	15950.1	2116.4	14.2
10	J	120-100-80	J	Standing	10	######	#######	#####	12.1	633.7	15139.7	18006.9	2867.2	17.3	15331.2	17815.4	2484.2	15.0
11	K	140-120-10	K	Standing	10	######	5647.9	75.2	0.4	23.8	19955.4	20062.9	107.5	0.5	19962.6	20055.7	93.2	0.5
12	L	150-130-11	L	Standing	10	######	#######	#####	12.3	801.9	18801.3	22429.5	3628.2	17.6	19043.6	22187.2	3143.6	15.2

Intraclass correlation coefficient (and 95% confidence limits) 0.849 0.722 0.944

Repeatability coefficient 4226.2
On 95% of occasions two readings should differ by no more than this.

Doppler area											For mean				For Bland Altman plot			
Group	Pressure_combinatio	Label	Symbol	Cofactor	Sample_size	Mean	Variance	SD	CV_pct	**Standard_error**	**Lower_CI**	**Upper_CI**	Length	Length_pct	**Approx_Lower_C**	**Approx_Upper_C**	Approx_Length	Approx_Length_pc
1	A	80-60-40	A	Sitting	10	5.5	4.0	2.0	36.5	0.6	4.1	7.0	2.9	52.2	4.3	6.8	2.5	45.2
2	B	100-80-60	B	Sitting	10	8.2	14.9	3.9	47.1	1.2	5.4	10.9	5.5	67.3	5.8	10.6	4.8	58.3
3	C	110-90-70	C	Sitting	10	16.0	21.3	4.6	28.9	1.5	12.7	19.3	6.6	41.3	13.1	18.8	5.7	35.8
4	D	120-100-80	D	Sitting	10	19.1	36.4	6.0	31.6	1.9	14.8	23.4	8.6	45.2	15.4	22.8	7.5	39.2
5	E	140-120-10	E	Sitting	10	7.3	5.0	2.2	30.8	0.7	5.7	8.9	3.2	44.0	5.9	8.7	2.8	38.2
6	F	150-130-11	F	Sitting	10	17.6	5.0	2.2	12.7	0.7	16.0	19.2	3.2	18.2	16.2	19.0	2.8	15.7
7	G	80-60-40	G	Standing	10	4.3	5.7	2.4	55.5	0.8	2.6	6.0	3.4	79.4	2.8	5.8	3.0	68.8
8	H	100-80-60	H	Standing	10	8.9	3.0	1.7	19.2	0.5	7.7	10.2	2.5	27.5	7.9	10.0	2.1	23.9
9	I	110-90-70	I	Standing	10	15.5	16.5	4.1	26.2	1.3	12.6	18.4	5.8	37.5	13.0	18.0	5.0	32.5
10	J	120-100-80	J	Standing	10	12.8	18.2	4.3	33.4	1.3	9.7	15.8	6.1	47.8	10.1	15.4	5.3	41.4
11	K	140-120-10	K	Standing	10	8.8	6.1	2.5	27.9	0.8	7.0	10.6	3.5	40.0	7.3	10.3	3.0	34.6
12	L	150-130-11	L	Standing	10	20.9	44.2	6.7	31.8	2.1	16.2	25.7	9.5	45.5	16.8	25.0	8.2	39.4

Intraclass correlation coefficient (and 95% confidence limits) 0.667 0.472 0.859

Repeatability coefficient 10.74
On 95% of occasions two readings should differ by no more than this.

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