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Non-invasive Time Sampled Venous Pressure Detection for Research and Clinical Applications

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A Thesis Submitted for

Doctor of Philosophy Degree

Work Conducted at
Bioelectronic Research Cluster
National Centre for Biomedical Engineering Science
National University of Ireland Galway, Ireland

And

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Abstract

The venous system of the lower limbs has unique anatomy that provides a skeletal muscle pump for the transport of blood against the hydrostatic gradient of erect postures. This muscle pump enables the regulation of venous pressures in the legs and is essential to maintain healthy tissue in the lower extremities. Chronic venous insufficiency and chronic venous ulcers are severe, related disease states associated with elevated venous pressures of the lower limb. The development and evaluation of new therapies for these diseases requires quantitative information about the haemodynamics of the venous system in normal, pathologic, pre-therapeutic, and post-therapeutic states.

The diagnostic methods and instruments for venous system evaluation and clinical diagnosis are reviewed with respect to their historical and contemporary capabilities and limitations. Their progression has moved toward non-invasive modes, culminating in the widespread use of duplex ultrasonography. The practice of duplex ultrasonography for the assessment of venous diseases leverages the structure, flow, and velocity data rendered by this technology. However, the observation of dynamic venous pressures with ultrasonography is not currently available, and there is an unmet need for non-invasive venous pressure capability congruent with duplex ultrasonography.

A novel method of assessing venous pressures using a time-sampled pressure probe (TSVPP) with ultrasonically imaged vessels is proposed. A set of requirements to define this instrument is developed from the vascular physiology and anatomy, and from the characteristics of contemporary ultrasound imagers. A proof-of-concept prototype is designed, fabricated and tested using artificial structures. The device and methods are optimized and then tested in animal models. A healthy human study is conducted using 12 volunteers.

The evaluation of the TSVPP in animal models demonstrated the feasibility of the instrument. $R^2$ fit values of 0.94 to 0.98 were achieved in Slow and Very Slow sampling modes. The results of the healthy volunteer study included 64 successful static pressure estimations from 72 observations. Over the 64 valid results, the mid and high pressure average error was within +/- 10%. Ambulatory venous pressure measurements were attempted using the slow sampling mode, and 5 of 9 attempts demonstrated a pressure recovery characteristic consistent with the classical ambulatory venous pressure response.
This thesis has explored a novel concept in venous pressure measurement and has extended the knowledge of its potential and limitations with qualitative and quantitative evidence. The results support an assertion that the TSVPP has promise for improving our insights into clinical diseases of the venous system. Further, the TSVPP can be developed as a useful tool for evaluating the effects of venous therapies designed to reduce venous stasis and hypertension. A foundation of conceptual work, bench evaluation, pre-clinical tests, and clinical study has been established. Future development of the concepts and implementations discussed appear justified from the potential intellectual, clinical, and societal benefits that can be associated with the product of this work.
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Dedicated to John and Margaret Kane

For demonstrating life with integrity, humor, endurance, and love.
Chapter 1
Introduction to the Non-Invasive Venous Pressure Probe
1.0 Introduction

For over a decade, the Bioelectronic Research Cluster at NUI Galway has been conducting a program of research on circulatory disorders of the lower limb and the design of Neuromuscular Electrical Stimulation devices and their application to enhance venous circulation and mitigate circulatory diseases [1-5]. Several therapeutic applications and their practical potential are currently being evaluated for their performance relative to standard clinical practices. The pathologies within the scope of these evaluations include post-operative deep vein thrombosis and chronic venous ulcers.

Within the group, and generally within the vascular clinician community, the primary venous circulation observation technique utilized is the ultrasound imaging of vascular structure and flow. Two ultrasound imaging modes are dominantly employed: Brightness Mode (B-Mode) and Colour Doppler Mode. Brightness mode imaging yields information about the underlying anatomy of the vessels and surrounding tissues [6]. Fine structures such as vessel walls are readily distinguished, and skilled practitioners can render the leaflets of the venous valve structures visible, both statically and in motion. Colour Doppler imaging renders blood velocity data that in combination with vessel geometry can produce flow measurements [7-9]. Flow data directly indicate venous circulation activity and can quantify the volume and rate of venous return. However capable the ultrasound instruments and the operators are, the observation of venous pressure is not available with conventional ultrasound imagers. Venous pressure data would be useful in the particular case of chronic venous leg ulcers, as the disease aetiology has been directly linked with elevated venous pressure [10, 11], and thus a primary objective of venous ulcer therapies is to reduce the venous hypertension or mitigate its effects [12-14].

Ideally, it is desirable to observe venous pressure non-invasively. Additionally, it is desirable to observe venous pressure with the currently available ultrasound instruments widely used in contemporary medicine.

Historically, a parameter called Ambulatory Venous Pressure (AVP) was considered the gold standard for the evaluation of patients suffering venous leg ulceration. The observation of AVP involves the direct cannulation of a vein in the lower limb and the use of a manometer to detect vessel pressure as it responds to a defined exercise. While simple in principle, the observation of AVP
requires a needle-stick with the concomitant discomfort and the small but inescapable risk of infection. AVP was largely replaced by photoplethysmography and more recently by ultrasound imaging in vascular clinics. Physicians have devised effective ultrasound techniques to inform the diagnosis and treatment of vascular disorders that result in venous ulcers, but neither photoplethysmography nor ultrasound techniques can provide direct venous pressure data.

However, the ability to ultrasonically image vein cross-sections at video frame rates opens the possibility to observe venous pressure by modifying the pressure outside the vein wall whilst observing the structural deformations [15]. The widespread adoption of ultrasound vascular imaging suggests that a pressure measurement system based on an ultrasound technique might have considerable utility. The ability to measure the instantaneous venous pressure, non-invasively, provides a physiologic parameter that will complement flow data and, for example, inform the dose-response relationship between lower-limb neuromuscular stimulation and the attenuation of venous hypertension in the lower limbs. It is the hypothesis of this thesis, that a practical instrument can be created that will augment the capability of ultrasonography to include the detection of static and dynamic venous pressures in superficial veins. An instrument of this nature would be a novel contribution to the field of diagnostic sonography by extending the capability of existing instruments to observe an important physiologic dimension in a non-invasive mode. The problem is multi-disciplinary, as the domains of ultrasonography, physiology, electronics, hydraulics, control systems, mechanics, and pre-clinical evaluations must be addressed to conceive and evaluate potential solutions.

1.1 Structure of the Thesis

Chapter 2 provides an overview of venous return from the lower limbs and describes the character, origin, and cycles of venous pressures. The clinical instruments available for observing venous pressure, the significance and history of Ambulatory Venous Pressure monitoring, and some contemporary alternatives to venous pressure observations are described. In Chapter 3, an instrument is proposed to non-invasively assess venous pressures of the lower limb. The instrument’s requirements and design parameters were established, based on the physiology of the system under
test and the established clinical indicators of pathology. As the instrument is novel, test structures had to be created to allow for the evaluation of prototypes *in-vitro*. These structures and the subsequent bench evaluations of the instrument are reviewed and analysed.

Chapter 4 describes the design, structure and results of *in-vivo* assessments conducted on animal models. The results of these studies are described and the implications of the results with respect to the development of a capable Time Sampled Venous Pressure Probe (TSVPP) are discussed.

In Chapter 5, a healthy volunteer study is described, and the results of static and dynamic venous pressure measurements are analysed. Finally, Chapter 6 contains an assessment of the results of these connected studies and the relationship between them. It concludes with a discussion of the improvements and future work for a clinically useful instrument.

This thesis has dual aspects. In one view, it is a record of academic pursuit and development with the proposition and the evaluation of a hypothesis. In another view, it is the foundation for a commercially useful implementation of the instrument that has been proposed. Appendix A contains many, but not all, of the original thesis concepts that been developed for submission as a patent or patents that will form the intellectual property foundation for a commercial implementation of this work. As confidentiality is a prerequisite for successful patent applications, only the contents of Chapter 2 of this thesis can be offered for publication at this time, and this work has been submitted to *Medical Engineering and Physics* for review.
Chapter 2
Techniques and Applications of Venous Pressure Measurements.

(Submitted for review to Medical Engineering and Physics.)
2.0 The Venous Circulation of the Lower Limb

This chapter will focus on the peripheral venous system of the lower limbs, the veins of the trunk, and the instruments and techniques for assessing the anatomy and function of the venous system.

Though the arterial and venous sides of the systemic circulation are complimentary facets of the same circulation, the venous system has features and functional complexities not found the systemic arterial system [16], [17]. By definition, the venous circulation begins at the return flow of the capillaries. The capillaries converge into venules, which further converge into veins. The veins become great veins, and finally the blood returns to the superior and inferior vena cavae before merging at the right atrium of the heart. The veins of the lower extremities are regularly interrupted by leaflet valves, which when patent, allow only unidirectional flow towards the heart. These valves are present in vessels as small as 18µm, however, they are most apparent in larger veins [18-20].

Veins in the lower limb are divided into the deep veins which traverse the interior volumes of skeletal muscle compartments, superficial veins that lie close to the skin, and perforator veins that allow the flow of blood between the superficial and deep veins (Figure 2-1). The combination of muscles, veins and valves creates structures known as peripheral muscle pumps. The compressive action of skeletal muscle contraction on the deep veins displaces blood. The directional characteristics of the leaflet valves ensure unidirectional venous flow (venous return) towards the heart. The veins refill from the capillary beds, and on subsequent muscular contractions, the process repeats. These peripheral muscle pumps are pervasive. They are found in the foot, the calves, the thighs, and the even the hands [21]. Peripheral muscle pumps are an essential element of a healthy venous circulatory system [22, 23].
An additional function of the venous system is that it acts as a variable reservoir of blood for the circulatory system. The capacity of the venous system allows the storage and release of significant blood volumes through the expansion and contraction of the vein diameters. An acute loss of 10% of the total blood volume can be accommodated, as well as substantial increases in blood volume [16].

The terminus of the systemic venous system is the union of the superior and inferior vena cavae, where the venous circulation flows into the right atrium. Though the venous pressures at the right atrium of a healthy individual vary over a small range, the total cardiac output can be substantially affected by small modulations of the right atrial filling pressure [17]. Right atrium pressure is synonymous with the term central venous pressure [24].

2.1 Venous Pressure

The pressure at any point in the venous system depends on myriad factors: Blood volume, cardiac output, posture, musculoskeletal activity, and venous tone are just a few significant influences. The total instantaneous pressure is affected by hydrostatic as well as dynamic influences. When standing or walking, the venous return from the lower limbs is dependent upon the action of the muscle pumps of the feet, calves and thighs [16, 25-27]. In the standing position, after a period of
inactivity, the pressures in the lower extremities are determined by height of the blood column [28]. During activity, the peripheral muscle pumps displace blood towards the heart and locally reduce venous pressure. Figure 2-2 illustrates the dynamic and static pressures of an upright individual. The pressure of the right atrium is labelled as zero, as this is typical of the filling pressure of a healthy individual. Central venous pressure (CVP) may drop to -2 mmHg during vigorous cardiac pumping or rise to 4-6 mmHg [29]. Pressures approaching 15-20 mmHg are usually indicative of severe heart failure. Compared to typical systemic pressures, the healthy individual has little variation in CVP.

Peripheral venous pressure can refer to a wide range of venous system locations, in particular the arms and legs. However, in clinical literature, peripheral venous pressure usually refers to a limb vein pressure that is correlated to the central venous pressure [30-35].

Ambulatory Venous Pressure (AVP) is the peripheral venous pressure value measured from a vein at the ankle or the dorsal aspect of the foot. This measurement uses a particular protocol that stimulates the muscle pumps of the lower limb. It evaluates effectiveness of the lower limb peripheral muscle pump system. Though it is not without shortcomings, it is considered to be a “gold standard” indicator for venous system function in the lower limbs [36-38]. Leaflet valve patency of the lower limbs and venous outflow obstructions are among the diagnostic observations possible with an AVP measurement [16, 39, 40].
Figure 2-2 Typical venous pressures. Hydrostatic pressure (HP) and Dynamic Pressure (DP) differ as a result of cardiac and venous muscle pump effects [16]. Posture, location, orientation and activity affect these values.

2.2 The Utility of Ambulatory Venous Pressure

The utility of AVP measurement is well established for the diagnosis of venous disorders [10, 16, 36]. Ambulatory venous hypertension, chronic venous insufficiency (CVI), venous ulcers, and venous thrombosis are conditions typical of the pathologies detected and differentiated using the AVP measurement. Ambulatory venous hypertension is the failure of the venous system pressure to fall during normal walking or during calf compression exercises. Ambulatory venous hypertension can be a consequence of venous thrombosis induced occlusions of the venous outflow tracts. It can also occur due to incompetence of the bi-leaflet valves in the venous muscle pumps. These conditions are associated with CVI, which is a term that describes a mosaic of lower limb venous system related pathologies. The symptoms include pain, swelling, oedema, telangiectasia, reticular veins, varicose veins, skin fibroses, hyperpigmentation, and ulcers [41-43]. Primary CVI is defined as a failure of
muscle pump function. Secondary chronic venous insufficiency is usually more severe and is associated with a combination of obstruction and reflux [43].

Chronic venous insufficiency is associated with skin ulcers of the lower limb. It is estimated that 70% to 85% result from CVI [44]. In the general adult population, the prevalence of venous ulcers is reported in the ranges of 1-2% [22]. The prevalence increases with age and is slightly higher in women than men [45]. The economic and social impact of this condition is substantial. The annual financial costs in the UK are estimated at $720 million and in the United States at $2 Billion annually [13]. The mortality associated with infections related to venous ulcers are estimated to be 2.5% [46].

Beyond the epidemiologic and financial considerations, the social isolation and pain associated with these pathologies is difficult to quantify in a way that reflects the personal suffering of individuals, yet there can be no doubt that severe ulcers are an affliction (Figure 2-3). Venous ulcers are painful, debilitating, persistent, and difficult to treat successfully. They have been recorded throughout the ages and cause substantial suffering, especially in the elderly [14]. The severity of chronic venous disorders can be categorized according to a clinical classification system referred to as CEAP (Clinical class, Aetiology, Anatomy, and Pathophysiology) [41, 47]. This system provides a uniform standard for evaluating venous disorders. The two most severe clinical classes, 5 and 6, denote the presence of healed or active venous ulcers.

Venous thrombosis is the formation of a thrombus in the venous system and can be either acute or chronic. Deep vein thrombosis (DVT) is the occurrence of a thrombus in the deep veins of the lower leg and can be caused by trauma, cancer, immobilization from injury, or surgical operations. Risk factors also include coagulopathies, smoking, oral contraceptive pills, and dehydration [48]. Regardless of the many causes of thrombosis, the consequences can be significant and sometimes life-threatening. Local symptoms include pain, swelling and tenderness of the affected limb [49, 50]. Venous thrombosis is a causative or compounding factor in many cases of chronic venous insufficiency. Unresolved, venous thrombus can cause occlusions of flow that can result in damage to the valves of the venous muscle pump. The combination of outflow obstruction and muscle pump damage is associated with the most severe clinical manifestations of CVI[43].
In addition to pain and infection risk, social isolation often accompanies the physical suffering from these recalcitrant ulcers [13, 51].

2.3 Ambulatory Venous pressure parameters

The AVP value is defined as the minimum pressure observed in a vein at the ankle or foot after a short series of heel raises, usually 6-10 paced at 1-2 seconds per heel rise [40]. A typical pressure time-course curve of a venous pressure test is shown in Figure 2-4. The minimum point on the curve is labelled AVP. AVP studies have provided excellent investigative and diagnostic results and have been a vital tool for the evaluation of normal and abnormal physiology of the lower limb venous system. The methodology of AVP measurement and the results have been the subjects of extensive study and discussion [10, 39, 40, 52-56].
A number of quantitative parameters are measurable beyond the single AVP value (Table 2-1). These parameters are extracted from the major landmarks of the AVP pressure tracing that occur before and after the exercise interval. Additional information can be obtained using mathematical analyses of the pressure curves during the exercise interval. These can be processed to separate the pressure increase and pressure reduction contributions from the venous reflux and muscle pump contributions [57].

**Table 2-1 AVP Parameters**

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<th>Acronym</th>
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<th>Description</th>
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<td>AVP</td>
<td>Ambulatory venous pressure</td>
<td>Minimum pressure observed after exercise interval</td>
</tr>
<tr>
<td>AVPr</td>
<td>Resting pressure</td>
<td>Full hydrostatic pressure observed after long duration of quiet standing without muscle pump activity (Typically &gt;60s)</td>
</tr>
<tr>
<td>AVPf</td>
<td>Fall in Pressure</td>
<td>(AVPr-AVP)</td>
</tr>
<tr>
<td>RT90</td>
<td>Recovery time to 90%</td>
<td>Interval from AVP back to 90% level of AVPr</td>
</tr>
<tr>
<td>PRI</td>
<td>Pressure relief index</td>
<td>(AVPf × RT90) A measure of overall venous function</td>
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Closely related to AVP is Continuous Ambulatory Venous Pressure Monitoring (CAVPM). This allows the observation of lower limb venous pressure on a continuous basis while the subject is free to
walk untethered using a monitor affixed to the lower leg. The technique allows collection of mean walking pressures and percent fall in walking pressure for improved assessments of chronic venous insufficiency [58]. The CAVPM technique is an extension of the accepted AVP method that leverages advances in the portability of electronics and sensors technology.

Though AVP is only one diagnostic technique available to clinicians and researchers, it has played a fundamental role in the development of a physiologic model for the evolution of venous ulcers and in the understanding of CVI [10, 59]. AVP remains useful for the differential diagnosis and identification of particular types of CVI. However, a fundamental limitation of the classical ambulatory venous pressure test is the need for invasive cannulation of the vein. While needle punctures are commonly practiced in medicine, they carry a finite risk of complications including bacteremia, phlebitis, and hemorrhage [60, 61]. In the case of AVP, the preferred locations for cannulation are near the common locations for ulceration. This proximity implies a heightened risk of infection. Non-invasive methods carry substantial appeal in this context, and a number of alternative diagnostic methods have been developed. Each has a unique set of advantages and deficiencies.

2.4 Pressure Measurement Instruments

Pressure measurement devices have evolved over time. The mercury manometer is time honoured, simple, and reliable. Though it is occasionally used as a gold-standard indicator, as a clinical pressure instrument, the mercury manometer has faded from general use. This decline started with the development of aneroid indicators, and has accelerated due to the availability of accurate and convenient electronic pressure transducers.

The aneroid indicators that remain in common use are similar to those shown in Figure 2-5(b, c) but in more modern forms. Contemporary technology provides precise, compact, and convenient pressure indicators using combinations of electronic transducers and digital display technologies. AVP measurements can be obtained using electronic pressure transducers, with the data display managed by a computer and easily converted to tabular or graphical form for analysis. Though the progression of manometer technology has been substantial, the improvements in the resolution,
precision, and convenience of the measurements do not address the fundamental unpleasantness and finite infection risk associated with the invasive needle stick required for venous access.

Figure 2-5 Progression of manometer instruments. Mercury type (a) circa 1910 [62]; Aneroid type(b) circa 1930[62]; Aneroid type(c) circa 1957[63]; Digital manometer (d) circa 2010.

2.5 Invasive venous pressure measurements

Central venous pressures, peripheral central venous pressures, and intracardiac pressures are related measurements commonly obtained with the use of an invasive cannula or catheter and a pressure indicator [34, 35, 64]. AVP is one variant of invasive pressure measurement techniques [30, 31, 65]. In AVP measurements, it is typical to cannulate a vein with a 21 gage butterfly needle that is coupled to a pressure indicator or transducer [10, 28, 66]. The earliest pressure indicators were often “U-tube” manometers, not very different from the type invented by Huygens. The liquid in the U-trap of the tube would displace proportionally to the observed pressure, and the change in the column height of the two legs of the tube was proportional to pressure difference between the vein and the atmospheric pressure present on the open side of the U-tube. Thus terms such as centimetres of water or mm of mercury owe their origins to the liquid displacement methods of measuring pressure. The density of the liquid affects the sensitivity of the U-tube manometer. For example, water displaces further than mercury for the same pressure difference, as the mercury has a density 13.5g/cc compared to 1g/cc for water. Thus 1 mmHg=1.35 cmH$_2$O.
2.6 Non-invasive pressure measurements

The development of many non-invasive pressure measurement techniques and instruments has been driven by the interests of patient comfort, the advantages of reduced infection risk, and the need for operational convenience. The simplest of these methods is the direct observation of superficial veins. For example, the distended jugular vein of a patient presenting with venous hypertension secondary to heart failure can be relatively easily observed (Figure 2-7). The distension of the jugular vein reflects increased central venous pressure beyond normal levels. While observations of this nature are useful, they remain imprecise and quantitatively ambiguous [67]. The effect of patient posture on the hydrostatic pressure offset, differences in vascular distensibility, depth of subcutaneous fat, and the variation of physician interpretation are some of several confounding factors the accuracy and reproducibility of this technique [24]. While the direct observation technique is an integral part of clinical assessment, the substantial lack of accuracy and precision it affords has motivated the investigation of many instrument-augmented techniques [68-74].
Among the most familiar non-invasive pressure measurement techniques, the auscultation blood pressure method is practiced in nearly every primary care medical facility in the world. This method employs controlled cuff-compression and auscultation to determine systolic and diastolic pressures in the brachial artery [76]. The classical instruments enabling this technique are the pressure cuff, the manometer and the stethoscope. Grouped together for auscultation, they are known as the sphygmomanometer. These have been in existence since the 19th century, and have evolved and improved over time [77]. The progression of these instruments is illustrated in Figure 2-8. This technique employs a pressure cuff that encircles the limb with the artery under observation. It also includes a bulb or pump to develop pressure in the cuff, and a pressure reading instrument to observe the cuff pressure. The interaction of pulsatile arterial flow with the open, partially closed and fully closed lumen of the artery produces signature acoustic signals known as Korotkoff sounds. The cuff pressures observed on the manometer correspond to the internal pressures of the brachial artery at specific shape transitions of the tested vessel. The classical method employed by clinicians uses auscultation enabled by a stethoscope on the artery. The electronic implementations of the
sphygmomanometer commonly include an automatic pump and pressure controller to drive the cuff. An acoustic sensor is employed to observe the Korotkoff sounds as the artery is cycled from unobstructed to occluded and back [78, 79]. The enormous popularity and endurance of the auscultation technique is attributable to its clinical significance and the accessibility of the data it can provide via non-invasive means. The success of this method for systemic pressure measurements is contingent upon the pulse pressure of the systemic circulation [80]. As the venous circulation lacks the substantial and periodic pulse pressure of the arterial system, Sphygmomanometers are ill-suited for venous pressure measurements.

![Sphygmomanometer](image)

**Figure 2-8: The instruments of Sphygmomanometry enable non-invasive arterial systemic blood pressure measurements.**

Substantial research has been carried out on the concept of using ultrasonography for the measurement of internal venous pressure by observing the shape, cross sectional area, diameter or other morphological characteristics of the vessel under evaluation. Most of this work has been directed toward the goal of improved non-invasive central venous pressure measurements. Lipton proposed the use of ultrasonography to facilitate detecting the transitional zone of the internal jugular vein where the local venous pressure is exceeded by the extravascular pressure resulting in a tapering venous cross-section. This is sometimes inaccurately referred to as a meniscus [81] [82]. His work improved visualization of the Internal Jugular Vein, provided greater accuracy, and good ultrasonic visualization results, even in the case of obese patients whose veins were obscured by adipose tissue. This technique was an elaboration of that proposed by Sir Thomas Lewis in 1930, but with the useful
enhancement of ultrasonic imaging [83]. Baumann et. al., reported central venous pressure measurements using the combination of external tissue pressure with ultrasonic imaging of the vessel [84]. This technique was a step beyond Lipton’s proposition, insofar as the apparatus applied pressure to the vein and observed the aperture of the lumen as it changed in response. However, the application of pressure was manual controlled by the operator. The apparatus used by Baumann is illustrated in Figure 2-9.

Figure 2-9 Ultrasound Probe (1) with attached fluid filled vessel(2), silicone membrane(3), and pressure tube(4) [84].
While the reported results exhibited significant differences between invasive CVP and non-invasive estimates, there was sufficient correlation to merit further refinement. Aggarwal et. al., continued this line of approach with a tissue pressure probe customized to facilitate manually controlled venous collapse with a digital pressure readout [85]. This was used concurrent with a handheld ultrasound probe. Its application is illustrated in Figure 2-10. Aggerwal’s approach used manual control of force, and the observation of venous morphology was realized with an ultrasound probe operating independently of a force sensor. The probe force was measured, and pressure was derived by factoring in the effective area of the probe. The observation of venous structure was not coaxial to the centre line of the force transducer, and as illustrated, two hands were required to align the system to the patient.

Figure 2-10  A force transducer used in combination with ultrasound transducer to estimate internal jugular vein pressure [85]
The pressure recording device created by Aggerwal depicted in Figure 2-11 included a microprocessor configured to record the transducer values when triggered by an operator. This allowed the operator to focus on the ultrasound image and the imaging technique, while storing the equilibrium pressure values without distraction. Limited evaluation data demonstrated consistent instrument readings, though no formal clinical data were presented.

Thalhammer et al., employed an apparatus similar to Baumann in a pilot evaluation of the non-invasive venous pressure technique applied to peripheral venous pressure. The study employed healthy subjects and intensive care patients with pressure observations taken at the forearm and
compared to a peripheral catheter measurement or a central venous catheter measurement. Good correlation was found, and R values of 0.95 and 0.85 were reported, respectively [15].

Other researchers have pursued approaches more similar to Lipton that use ultrasound for observation without an associated pressure instrument. Simon et al. compared the cross sectional areas of the internal jugular vein at rest and with the Valsalva manoeuvre. The results of a 67 subject trial were favourable for the detection of elevated right atrial pressures, with 90% sensitivity and 74% specificity [70]. However, the results were not quantitative pressure values, but instead, returned a true/false clinical indicator of clinically significant elevated pressure. While potentially useful for the specific question studied [73], the technique has limited application to the general venous circulation.

Bigler et. al., attempted to correlate the respiratory variation of jugular vein diameter observed using ultrasound to the central venous pressure. This variation was quantified by two mathematical relationships calculated using the maximal internal height and width of the IJ vein and the minimal height and width if the IJ vein, as these dimensions changed with respiratory mediated pressure variation.

\[ \text{Collapsibility Index: } \frac{((\text{MaxHeight} \times \text{MaxWidth})/2) - ((\text{MinHeight} \times \text{MinWidth})/2)}{((\text{MaxHeight} \times \text{MaxWidth})/2)} \]

\[ \text{Distensibility Index: } \frac{((\text{MaxHeight} \times \text{MaxWidth})/2) - ((\text{MinHeight} \times \text{MinWidth})/2)}{((\text{MinHeight} \times \text{MinWidth})/2)} \]

The results showed that a fair to moderate correlation could be observed between jugular distensibility and CVP [86].

Keller et. al., attempted ultrasound imaging of the internal jugular vein and concluded that a CVP greater than 8 mmHg could be accurately estimated with ultrasound assisted observations of the jugular vein aspect ratio (ratio of IJ height to width)[87]. Siva et al continued on the line of Baumann and demonstrated good sensitivity and specificity of CVP measurements via ultrasound enhanced visualization of the blood column height in the internal jugular vein [88].

Lisiecki et al. extended the technology of jugular vein pressure estimation by dimensional observation with the design of a dedicated ultrasonic monitoring patch [89]. The concept employed dedicated ultrasound transducers and control electronics on an adhesively mounted detection assembly. In principle, the power source, computational hardware and readout were integrated into a convenient assembly. However, there is no record in the patent application of successful prototypes or
further development activity. Independent of the maturity of the technology, this instrument is limited by the indirect approach of estimating pressure by jugular vein diameter.

![Figure 2-13 A. Central Venous Pressure measurement apparatus employing ultrasound to estimate venous pressure by observing jugular vein diameter. B. Proposed application by adhesion to the skin over the jugular vein [89].](image)

### 2.7 Alternatives to Ambulatory Venous Pressure Measurements

Approaches to the assessment of venous physiology, anatomy and pathophysiology have been developed that compliment and sometimes supplant the direct assessment of pressure using the AVP method. These have been motivated in some part to provide anatomical information that AVP does not, or to obtain functional information of similar value in a non-invasive manner. A non-exhaustive list of these approaches includes photoplethysmography, ultrasonography, air plethysmography, venography, contrast computed tomography, and magnetic resonance venography. Several variations are available within these approaches. A short description of each follows to highlight the character of the information provided.

Photoplethysmography (PPG) was developed by Hertzman in the 1930’s [90, 91]. The PPG instrument shines infrared light into the tissues and measures the reflected or transmitted signal (Figure 12). The amplitude of the signal changes with the quantity of haemoglobin in the tissue and indicates perfusion. This technique became practical for widespread adoption following advances in solid state electronics in the 1970’s and 80’s [92, 93]. While dual wavelength PPG is commonly used to measure heart rate and oxygen saturation, the photoplethysmograph has also been adapted to measure the perfusion of the lower limb. The PPG approach has been evaluated as an alternative to
conventional AVP and other plethysmographic techniques to evaluate venous haemodynamics. For example, PPG can be used to show the refilling characteristic of the classic AVP pressure response based on the changes in tissue perfusion concomitant with refilling. However, though the recovery times can be observed, venous pressure cannot be quantified directly.[94, 95]. PPG can also be used to observe venous reflux and, in combination with a pressure cuff or tourniquet, differentiate the relative contribution the of deep and superficial venous systems [96] [97]. However PPG is not widely used and it suffers from limitations of specificity, calibration issues and tissue pigmentation effects [16, 98].

Figure 2-14 Photoplethysmograph in use [99]

Strain gage plethysmography (SGP) and air plethysmography (APG) are related methods of quantifying limb volume and are indicators of venous filling and perfusion. The former method uses a circumferential transducer that converts a gauge length (usually the circumference at one or more points on a limb) into an electrical signal. This signal is converted and computed to produce a volume measurement. The Air Plethysmograph employs a cuff surround the limb with a closed air space (Figure 2-15A). Pressure in the cuff is set to 6 mmHg prior to testing [96]. During testing, changes in
the cuff pressure as the limb varies in total diameter are converted to electrical signals which are used
to estimate volume changes. APG can be used to measure muscle pump ejection fraction, reflux, and
venous volume [97]. The strain gauge plethysmograph (Figure 2-15B) can be used to observe calf
volume and venous outflow rates [100, 101]. SGP and APG both provide venous refilling time
information. Each can be used in combination with tip-toe exercises and tourniquets to identify reflux
and the deep or superficial system contributions to reflux. Confounding influences on the resulting
data include patient position, stability, weight-distribution while standing, and the quality of the tip-
toe exercise performed for the evaluations [16].

Figure 2-15 Air plethysmograph in use (A) [96], Strain Gauge Plethysmograph used to measure calf volume (B).

Ultrasonography has become a mainstay diagnostic resource for evaluating venous disorders of
the lower limb [102, 103]. The precision and scope of ultrasonic imaging techniques have expanded
significantly in the last several decades. Modern ultrasound imaging includes brightness mode
imaging (B-Mode) and Colour Doppler imaging. B-Mode is typically represented as a black and white
moving image that offers real-time visualization of internal physical structures. In this mode,
ultrasound offers structural definition of the blood vessels, tissues and organs of the body. Vein walls,
diameters, shapes, and dimensions are easily observed. Arteries are readily distinguished from veins
by their pressure insensitive diameters and the presence of pulsatile motion. B-mode ultrasound
provides the operator with the ability to visualize the anatomy of the vascular system. The use of
handheld probes is common; as these allow investigators to focus on specific structures. The non-
invasive nature of ultrasound scanning and its freedom from contrast agents used in phlebography are perceived advantages [104]. However, the general scope of visualization is limited, and concurrent visualization of a limb’s venous network is not possible.

Colour Doppler mode ultrasound technique allows the blood velocity in a vessel to be measured. The blood velocity data is typically superimposed onto the B-mode image. Colour coding the sign of the velocity vector allows the operator to easily observe normal and reversed flow directions [105]. In combination with vessel diameter measurements achieved with B-mode data, the Doppler data enables the calculation of flow rates. These can be integrated over time to render average flow, total flow etc. The combination of the colour Doppler and B-mode techniques is commonly referred to as duplex ultrasound. Duplex sonography has demonstrated excellent sensitivity and specificity for the detection of deep vein thrombosis [16] and can be used to observe venous stasis, occlusion and reflux [106, 107].

Contrast Venography is a method of visualizing a segment of the venous system by a combination of marker injection and radiography (Figure 14). The approach is invasive, as cannulation is a requisite element of the contrast dye injection technique [16]. The dye introduces a risk for allergic reaction, vessel injury, or thrombosis that has been reported at rates as high as 3% [108]. The need for fluoroscopic imaging adds the complexity and cost of X-ray equipment to the method. Descending venography can identify the location and extent of valve incompetence [109]. Ascending venography can identify vein patency and incompetent perforator veins [110]. Dye mixing, weight bearing on the studied leg, and poor injection site selection can confound this technique. The need for venography has been reduced with the advent of Duplex Ultrasonography [108, 111].
Contrast computed tomography (CT) and magnetic resonance imaging (MRI) venography offer the unique feature of 3-dimensional visualization. These are advanced imaging modalities, but they entail the high cost and complexity of the highly capital intensive equipment. A CT scanner can cost from $400,000 to $1,5000,000 to install with annual maintenance costs of $100,000 or more [112]. MRI scanners are more expensive, with machines in the range of $1,5000,000 to $3,000,000 without maintenance or infrastructure support costs included [113]. These instruments also have significant safety concerns. Ionization radiation dose is substantially greater for CT than for other X-ray modalities, and studies have concluded that while CT scans are a very small fraction of all radiologic examinations, they contribute 35% to 45% of the total radiation dose of the medical patient population [114]. CT X-ray dose reduction and safety are areas of concern and the focus of much investigation in the radiologic community [115-117]. MRI scanning wholly avoids the ionizing radiation concern, but the extreme magnetic fields and strong radio frequency fields contraindicate the method for patients with many types of orthopaedic and cardiovascular devices who might otherwise benefit [118]. While the imaging and diagnostic capability of these modes are unique, the high cost of these diagnostic systems places them in a separate category from portable duplex scanners, manometers, and plethysmographs.
2.8 Conclusion

The systemic venous system has a unique constellation of structures and haemodynamic behaviours. The interaction of valves, veins, and the musculature of the limbs enables efficient venous return back to the heart. When the normal return functions of the venous system are interrupted through venous obstruction, valvular incompetence, or other pathologies, the symptoms and sequelae can be severe. The incidence, quality of life impairment, and societal costs of chronic venous insufficiency, deep venous thromboses, and venous ulcers are significant.

Medical instrumentation has enabled substantial progress in the understanding and treatment of venous diseases through the reliable observation of vascular structures and their haemodynamics. Table 2-1 summarizes the range of vascular instrumentation, techniques, and capabilities. Much has been learned from invasive measurements like ambulatory venous pressure (AVP). AVP is able to provide an overall assessment of the efficiency of the calf muscle pump, it correlates well with the incidence of venous ulceration, and it may also correlate with the clinical severity of venous disease. However, the advent of non-invasive alternatives has displaced AVP from general use. Plethysmographic techniques offer an alternate measure of AVP refilling times, but are cited for lack of specificity, among other drawbacks. Duplex ultrasonography has become a mainstay of the diagnostic approaches and has largely displaced venography for general venous imaging. Duplex sonography offers structural information and flow data, but unassisted, it does not provide venous pressure data. Newer imaging modalities such as CT and MRI have economic, safety and accessibility constraints that limit their broad use for lower limb venous disorders.
<table>
<thead>
<tr>
<th>Technique</th>
<th>Instrumentation</th>
<th>Diagnostic Parameters</th>
<th>Notes</th>
<th>Invasive</th>
<th>Cost</th>
<th>Anatomical Imaging</th>
<th>Flow Visualization</th>
<th>Quantitative Pressure</th>
<th>Qualitative Flow</th>
<th>AVP Refilling Times</th>
<th>AVP Pressure Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jugular Vein Observation</td>
<td>None</td>
<td>Clinical sign</td>
<td>Non-quantitative, highly technique dependent.</td>
<td>No</td>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AVP</td>
<td>Cannula, manometer</td>
<td>Direct pressures including resting and dynamic pressure parameters</td>
<td>Quantitative and accurate. No flow rate data. No structural imaging.</td>
<td>Yes</td>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Plethysmography</td>
<td>Air Plethymograph, Strain Gauge Plethysmograph, Photo Plethysmograph</td>
<td>Pressure Recovery time</td>
<td>Neither flow rate nor pressure data</td>
<td>No</td>
<td>Low</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Duplex Ultrasoundography</td>
<td>Ultrasonic imager</td>
<td>Visualization of venous structures and flow. Flow velocities and rates</td>
<td>No pressure data</td>
<td>No</td>
<td>Med</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>x</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Contrast Venography</td>
<td>Fluoroscope, cannula, contrast medium</td>
<td>Visualization of venous structures and flow.</td>
<td>No quantitative flow or pressure data</td>
<td>Yes</td>
<td>Med</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Contrast Tomography</td>
<td>CT scanner, contrast medium</td>
<td>Visualization of venous structures and flow.</td>
<td>Visualization can be superior to sonography</td>
<td>Yes</td>
<td>High</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>MRI Venography</td>
<td>MRI system</td>
<td>Visualization of venous structures and flow.</td>
<td>Obviates the need for contrast agent</td>
<td>No</td>
<td>High</td>
<td>x</td>
<td>x</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Proposed Non-invasive Venous Pressure Probe</td>
<td>Ultrasound imager, acoustically transparent dynamic pressure adaptor</td>
<td>Visualization of venous structures and flow. Flow velocities and rates</td>
<td>Proposed system and method</td>
<td>No</td>
<td>Med</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Though the current suite of diagnostic instruments available to the clinician is diverse and capable, the non-invasive measurement of venous pressures and the non-invasive measurement of Ambulatory Venous Pressure are observational modalities that are currently unmet. Both the academic literature on non-invasive venous measurements and the patent literature focus on Central Venous Pressure techniques and applications. There are no devices described in either domain that attempt to either statically or dynamically assess lower limb pressure or record ambulatory venous pressure parameters. While no single measurement is capable of grading the clinical severity of
Venous Disease and fully informing the diagnosis, the current suite of measurements lacks convenient and safe access to the historical ‘gold standard’ of AVP. A device that would provide AVP data non-invasively would allow researchers and clinicians to complement structure and flow data with temporally accurate pressure information and is sure to find general clinical utility.
Chapter 3
Design of a Non-Invasive Time-Sampled Venous Pressure Probe
3.0 Introduction

As discussed in Chapter 1, the current, routine performance metrics used for the assessment of the efficacy of NMES-assisted venous return for the management and treatment of venous leg ulcers are changes in Popliteal venous velocity and changes in Popliteal volumetric flow rates [7]. However, it was also noted in Chapter 1 that the primary objective of NMES-assisted venous return in venous leg ulcer applications is to produce a reduction in venous pressure at the lower leg and thus ameliorate venous hypertension and its associated complications [119, 120]. The adoption of venous pressure at the lower leg as a new metric for this assessment would require the non-invasive measurement of venous pressure. In other words, it would require the measurement of venous pressure without the need for the insertion of a venous cannula.

Figure 3.1 shows an idealized graph of ambulatory venous pressure in two subjects. Plot A represents a subject with intact venous return, and Plot B represents a subject with compromised venous return and subsequent venous hypertension. Ideally, with the adoption of venous pressure as our new metric, we would like to be able to reproduce ambulatory venous pressure records of this type. In combination with the venous velocity and flow rate data that are accessible using duplex ultrasound, the velocity, flow, static and dynamic pressure data would constitute a comprehensive parametric measurement set with the potential for improved diagnostic capability.
Figure 3.1 Idealised Ambulatory Venous Pressure recordings from the lower leg. (A) A patient with intact venous return has a slow refilling rate, as veins are refilled from capillary flow. (B) A patient with compromised leaflet valves shows rapid refilling times, as reflux past the leaflet valves contributes to vein refilling.

This chapter describes the design of a non-invasive Time-sampled Venous Pressure Probe (TSVPP). The basic operating principles of the TSVPP are that it applies a programmable external pressure to the superficial vein under test while simultaneously capturing the B-mode ultrasound image. The observed changes in the vein morphology are correlated to the applied external pressure at each instant in time. (Each video frame has a pressure signature). When the pressure outside the vein is less than its internal pressure, the vein cross-section will be generally circular, and the vein walls/lumen will be well-defined in contrast to the surrounding tissue. However, when the pressure outside the vein exceeds its internal pressure, the vein will be seen to collapse, the lumen will disappear from view and the vein walls will blend in with the surrounding tissue. The external pressure applied when this change in the appearance of the vein occurs can be recorded as a good approximation of the venous pressure at the moment at that location (Figure 3.2). Since the B-mode
ultrasound image is acquired using a modern ultrasound system, the Doppler velocity and flow data measuring capability are integrated features of the imager. Thus the observation of flow, velocity and pressure characteristics are possible using the same instrumentation.

Figure 3-2 Non-Invasive Pressure Observation Principle: (a.) illustrates a vein whose internal pressure is in excess of that of the pressure chamber (b.) The chamber pressure has been raised above that of the resting vein pressure and the vein has collapsed.

As noted in Chapter 2, the operating principle on the use of an external pressure to observe venous pressure with ultrasound was first demonstrated statically on central venous pressure by Aggarwal et al in 2006 [85] and Thalhammer et al in 2007 [15]. The pressure readings these researchers obtained strongly correlated with central venous pressure readings. However their methods were entirely manual with respect to the probe and diaphragm pressure. There was neither automatic control of the external pressure modulation, nor was there any mention of time sampling or dynamic pressure observations in their work.

3.1 Time Sampled Venous Pressure Measurement

As a key contribution, the TSVPP extends the basic principle proposed by Thalhammer et al and Aggarwal et al by automatically modulating the external pressure outside the vein in a periodic manner to enable time sampled data of venous pressure. These data can be reconstructed to provide observations and records of time-varying venous pressure. For example; a desired application of the TSVPP would be to record the refilling times of the lower limb vasculature following excitation of the calf muscle pump. This could enable multi-parametric evaluations of the hemodynamic impact of
voluntary contractions relative to pneumatic compression, or neuromuscular electrical stimulation mediated contractions.

A flow chart of the proposed TSVPP in one several possible modes of operation is shown in Figure 3.3.

![Flow chart of the proposed TSVPP](image)

**Figure 3-3 Proposed TSVPP operating principle:** A commercial ultrasound system provides a B-mode video image of a target vein. The external venous pressure is increased. The response of the target vein observed for changes representing pressure equilibrium. The external pressure value is captured at the equilibrium instant along with the vein image. The external pressure is released and the cycle repeats generating a time-series of pressure values.

The essential components of the proposed system are as follows: a Diaphragm Pump (which involves a Pressure Chamber, a Piston Actuator and a Silicone Vessel), a Pressure Sensor (measuring pressure within the Silicone Vessel), an Ultrasound Probe configured to image through the silicone vessel, and a microcontroller-based Electronics System which is used for pressure signal acquisition and Diaphragm Pump control. The system operates by periodically cycling chamber pressure from low to high and back again to facilitate periodic occlusion of the vein under test. The assembly is designed to enable ultrasound imaging to occur through an acoustically transparent liquid filled Pressure Vessel. (Similar in concept to Thalhammer and Bauman, however this pressure vessel is pumped.) This allows the operator to observe the vein occlusion when it occurs. A video feed from the ultrasound equipment is collected in parallel with chamber pressure signal and stored on a recording computer.

Cycling of the chamber pressure must occur at a sufficient rate to enable accurate reproduction of the vein pressure waveform. To achieve this using the time-sampled approach, we need to assess the frequency characteristics of the signal to be sampled and the mechanical & hydraulic frequency limitations of the Diaphragm Pump.
3.1.1 Spectral Characteristics of the Ambulatory Venous Pressure Signal

Figure 3-1 illustrates the time-domain ambulatory pressure waveforms typical of healthy and pathologic patients. The “calf exercise” segment of the curves (when venous pumping is occurring with a consequent reduction in venous pressure) contains the highest frequency content for this signal. Temporal analysis reveals that the spikes in the calf exercise section of the waveform (each spike corresponding to a contraction of the calf muscle) exhibit a fundamental frequency of approximately 1Hz. The sharp edges on the pressure spikes, indicate harmonics that may be 3\textsuperscript{rd}, 5\textsuperscript{th} and higher orders. These pressure spikes are superimposed on the falling edge of a much slower signal, the average lower limb venous pressure.

For the purpose of evaluating peripheral venous valve patency, the magnitude of the pressure drop and the length of the refilling time are the data of greatest diagnostic and clinical interest. These parameters are observed at low frequencies. When the rapid fluctuations of the calf exercise segment of the waveform are ignored, the bandwidth of signal can be approximated using the duration of the falling edge of the pressure signal, which is 6-8s. If we use a 6s estimate for the falling edge, the signal bandwidth of the pressure waveform is determined using Equation 3.1.

**Equation 3.1 [1]**

\[
\text{Bandwidth of Pulse Waveform} = \frac{0.35}{\text{Minimum (Rise Time (s), Fall Time(s))}} \text{ Hz} = \frac{0.35}{6} \approx 60 \text{ mHz}
\]

Following the well-known Nyquist-Shannon Sampling Theorem [121, 122], sampling rate must be greater than twice the bandwidth of the signal of interest. Thus the minimum sampling frequency for the pressure waveform is 0.12Hz. This is easily achieved electronically with a minimum specification analogue to digital converter. However, the hydraulic and mechanical elements of the proposed system (briefly described in Section 3.1) will influence the overall system-sampling rate by setting lower-limits on the minimum interval at which the chamber pressure can be cycled.

3.1.2 Time Sampling of the TSVPP
The analysis of the frequency content of the venous pressure signal and the frequency limitations of the mechanical & hydraulic system indicate that a minimum sampling frequency of 0.12Hz. Typically over-sampling is applied to relax the reconstruction filter requirements and improve signal to noise ratios. The ultrasound imager frame rates can vary with the choice of imaging parameters, but 15Hz is the minimum image rate used in these studies.

Figure 3-4.4a shows a typical continuous time ambulatory venous pressure (AVP) waveform with annotations describing the major features. Figure 3-4.4b shows the TSVPP pressure chamber waveform superimposed on the AVP curve. The intersections of the AVP with the rising edges of the chamber waveform are marked with circles. It is at these chamber pressure points where the vein will collapse observed using the B-mode ultrasound imager. The benefits of over-sampling are illustrated by comparing Figure 3.5(a) and (b). The former figure is sampled at 0.15Hz, close to the calculated Nyquist frequency of 0.12Hz. While the major features of the waveform are present at this sampling frequency, the benefits of over-sampling are readily apparent in the 0.3Hz data set (2.5 over-sampling rate).

![Figure 3-4 Ambulatory Venous Pressure waveform(a); With a TSVPP chamber pressure waveform superimposed (b).](image)

![Figure 3-5 Ambulatory Venous Pressure reconstructions. Data sampled at 0.15Hz (a), and at 0.30Hz (b). Time units in seconds and Pressure units in mmHg. Both plots suggest the continuous time curve of the AVP waveform, but the 0.3Hz rate allows more accurate temporal reconstruction.](image)
3.1.3 Mechanical/Hydraulic Frequency Limitations

The mechanical and hydraulic frequency limits of the system are set by the servo mechanism of the TSVPP. In principle, a system could be conceived with low-inertia mechanical components, high torque drive motors, and short stroke lengths for the diaphragm displacement. This combination would allow high rate mechanical cycling of the diaphragm. However, practical considerations for the overall TSVPP size, power and cost limitations constrain the design. Available, compact servo motors have angular velocity limits that bound the pump assembly to stroke repetition rates in the range of 1-4Hz. Based on the analysis of the signal spectral content, an oversampling ratio of 8-33 may be achieved, rendering satisfactory reconstruction of the signal.

3.2 Target Operating Characteristics of the TSVPP

As a primary objective for this work is to explore the creation of a credible alternative to AVP measurements obtained by cannula and manometer, AVP measurement values typically obtained under clinical conditions can inform the useful reference operating characteristics for the design proposal. The AVP measured at the dorsal foot vein ranges from approximately 100mmHg to 22mmHg, depending on the person’s height, vascular patency, recent exertions, posture, etc. Normal subjects exhibit a drop in AVP to a minimum value in about 10 seconds while performing sequential heel-raises. The pressure recovery rate is normally slower, and healthy individuals may take 30-40s for the AVP to return to static standing levels. However patients with severely compromised vasculature may have AVP recovery intervals as short as 3-5s [36]. These AVP signal characteristics have been combined with fundamental safety and comfort concerns (Table 3.1) to establish Operating Characteristics for the TSVPP device.

<table>
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<th>Index</th>
<th>Application Requirement</th>
<th>Target Specification</th>
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<tbody>
<tr>
<td>1</td>
<td>Patient safety</td>
<td>Double isolation with medical grade power supply or battery</td>
</tr>
<tr>
<td>2</td>
<td>Patient comfort</td>
<td>Non irritating, smooth and burr-free assembly</td>
</tr>
<tr>
<td>3</td>
<td>100mmHg max pressure</td>
<td>140mmHg</td>
</tr>
<tr>
<td>4</td>
<td>22mmHg min pressure</td>
<td>15mmHg</td>
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<tr>
<td>5</td>
<td>Observe 80mmHg pressure drop in 10s</td>
<td>Max sampling rate of 1Hz</td>
</tr>
<tr>
<td>6</td>
<td>Observe 80mmHg pressure rise in 5s</td>
<td>Max sampling rate of 1Hz</td>
</tr>
<tr>
<td>7</td>
<td>Observe full AVP test cycle ~45s</td>
<td>Data capture up to 60s</td>
</tr>
<tr>
<td>8</td>
<td>User Comfort</td>
<td>Ergonomic fit to the hand with comfortable control placement</td>
</tr>
</tbody>
</table>
3.3 System Design

3.3.1 System Architecture Development

The proposed instrument requires several functions operating together such as a programmable pressure source, instantaneous pressure readout, and a concurrent record of pressure, time, and the venous wall condition (collapsed or open). A number of possible architectures were posited, with various approaches to pressure readout design, pressure vessel design, and ergonomics.

A fundamental element of the TSVPP concept, as proposed, is the use of ultrasonic imaging. The Logiq-e ultrasound scanner that was available for this work included motion-picture capture. A pressure readout that could be imaged ultrasonically was one approach considered to leverage that feature. The result would be a simple system with a single data record of pressure and morphology that could be reviewed on the ultrasound playback system. The readout was intended to reside in TSVPP housing, within the pressure vessel or directly between the vessel and the chamber housing.

In a direct mechanical sensing and readout structure, a beam array of various lengths was proposed to lie within one portion of the B-mode imaging field. The pressure vessel would communicate the instantaneous pressure to the beams, and the cross members would collapse in order of decreasing beam length (Figure 3-6). The collapse would cause acoustic reflections to be detected on the B-Mode display that varied with pressure, and these would be recorded with the vein images. The intended result was a pressure bar-graph that would display concurrently with the vein images. This mechanical approach was abandoned due to the difficulties of fabrication and the limited pressure resolution of the discrete bar concept. Instead, a commercial pressure sensor was selected for its precision, accuracy, and durability.
Figure 3-6 Direct mechanical ultrasonic readout. (a) Top view of a support layer and indicator bar. Each element is 0.5 mm thick. (b) Deflection beam layer shows horizontal bars also about 0.5mm thick. These can be made from plastic; for example Delrin. (c) Top view of the readout shows the cover layer over indicator and deflection beam layers. The cover layer communicates pressure onto the supporting beams causing them to move. (d) Deflection beams in relaxed state (top) and deflection beam in contact with indicator bar from applied pressure(bottom). The ultrasonic impedance of the structure changes abruptly when the deflection beam couples or decouples mechanically with the indicator bar in response to applied pressure. The space between the cover layer and the supporting layer (grey) is open to atmospheric or another fixed reference pressure.

The first generation TSVPP housing design included a narrow aspect pressure vessel with an integrated elliptical aperture for the diaphragm, a hinge type displacement pump, and a slot to accommodate mechanical pressure readout (Figure 3-7). The integrated diaphragm aperture made the housing fragile. The pump mechanism was unreliable, and the pressure indicator was abandoned for a reliable commercial device. The second generation housing demonstrated similar deficiencies.

Figure 3-7 Two views of the first generation TSVPP prototype. (a) Housing with ultrasound probe in place. (b) An elliptical diaphragm port with fracturing apparent in the thin sections of the SLA material.
Pump reliability and durability problems were resolved by the third mechanical prototype. This included a bonded stainless steel baseplate, a large circular diaphragm aperture and a piston type pump assembly. The aperture, pump and pressure sensor redesigns necessitated an improved silicone pressure vessel. Moulds were created to cast custom thin-wall silicon chambers that were fitted with a reinforcing tube to accept the direct placement of the pressure sensor. This consisted of a commercial grade silicone tube passed through a hole formed in one face of the vessel. The tube was bonded with medical adhesive to the silicone walls, and trimmed to length after curing. The final pressure vessel is depicted in Figure 3-8.

![Figure 3-8 Final pressure vessel design with sensor in place. The vessel is filled with degassed mineral oil and sealed. The pressure sensor is inserted into a reinforced tube at one end.](image)

The selection of an electronic sensor and the development of an acceptably reliable and durable diaphragm and pump assembly allowed the remaining system elements to be configured. Figure 3-9 depicts the functional block diagram of the system over the physical block diagram of its major components.
The Target Vein

Figure 3-9 System Proposed TSVPP Block Diagram: A commercial ultrasound system is coupled to the Diaphragm housing acoustically and mechanically, while the B-mode video stream is coupled to a recording computer. The pump and pressure sensor are driven from the Control board and communicate data via USB to the recording computer. The target vein is interrogated ultrasonically for morphology and mechanically via the diaphragm pump for pressure.

The Time-Sampled Venous Pressure Probe (TSVPP) intended for use in conjunction with a standard medical ultrasound scanner. Much of the system design is focused on the interface between the TSVPP and the ultrasound instrument. The acoustic transducer, the TSVPP housing and the connections between the recording computer and the ultrasound video port are customized for physical and electrical compatibility. The final prototype was configured to accommodate a GE Logiq-e scanner. The 8L and 12L linear array vascular imaging probes have identical form factors and both are compatible with the TSVPP. The imaging probe contours define the inner geometry of the TSVPP housing, and to a lesser extent, the outer configuration of the instrument. Figure 3-10 depicts the ultrasound probe fitted into the final prototype instrument housing.
The combination of the 1Hz pressure-sampling target specification with the working pressure range of 125mmHg requires rapid vessel pressure slew rates. The acoustically transparent fluid chamber must pump from 15 to 140mmHg in 0.5 seconds, while the interfaces between the chamber, the imaging probe, and the tissue remain acoustically coupled. The pump rate is realized with high torque servo driving the piston proximal to the diaphragm. The pump has been created within the TSVPP housing itself. The pressure chamber generally operates with a positive pressure that maintains contact between the silicone vessel walls and the tissue or ultrasound probe. Ultrasound imaging gel is used at both interfaces and effectively maintains acoustic coupling during operation.

Directly ported into the diaphragm fluid vessel is a precision pressure sensor (Honeywell type 26PCB) with a custom electronics package to read back data. This electronics assembly also accepts user input and controls the pump motion. The electronic functions include bi-directional USB communications link, analogue to digital conversion, pulse- width modulated servo control and user input processing. Together, these signals and controls integrate the sensing, computational, mechanical and hydraulic elements of the system. The image data are independently rendered by the
ultrasound scanner and simultaneously displayed on the scanner. The real-time video stream from the ultrasound is captured by an Epiphan VGA2USB LR™ frame grabber and the data are stored on an external computer. These image data contain the important morphological record of the venous walls and the images of the tissue proximal to the observation site.

The overall TSVPP instrument is not as compact as the GE 8L/12L ultrasound transducers, but the extra bulk houses the transducer, pressure sensor, and pump, and is designed to fit an average-sized hand so that the combination can be manoeuvred effectively.

### 3.3.2 System Mechanical Design

The instrument housing is shown in Figure 3-10. It contains cavities for the ultrasound transducer, the fluid vessel, and the pressure sensor. A rigid housing was modelled in Solidworks and constructed using SLA (Stereo-Lithographic-Apparatus). This enabled the fabrication of the conformal receiver for the ultrasonic probe that is acoustically and mechanically coupled to the fluid vessel and pump assembly. A cross-sectional view of the HVPP assembly is shown in Figure 3-11 with labels naming the important features. The housing includes mounting bosses for a servo motor and a friction bearing for the pump plunger. The ultrasound transducer is positioned above the fluid vessel and the facing surfaces are intimate. The conformal shape of the transducer cavity, along with four retainers, ensures positional stability of the ultrasound probe. In operation, a small quantity of ultrasound gel is applied to the interface of the probe and the fluid vessel. This optimizes the acoustic coupling between them.
Figure 3-11 Cross sectional CAD view of the TSVPP housing assembly. The fluid vessel is not depicted, but resides in the space below the ultrasound transducer and above the base plate. The piston rod is capped by an SLA formed piston head that is sized to push the entire end face of the fluid vessel. This maximizes displacement for the available stroke length.

Figure 3-12 provides a top view of the housing, looking through the cavity that contains the ultrasound probe. Nearly the entire top surface of the fluid vessel is exposed. In use, the ultrasonic transducer face meets and constrains this vessel surface. The aperture plate can be seen on the bottom of the fluid vessel. This is a thin stainless steel plate with a large circular opening (29mm diameter).
which allows the bottom surface of the vessel to act as a distensible diaphragm which communicates the vessel pressure into the local tissue.

![Figure 3-13 TSVPP Housing underside with aperture and extended diaphragm On the right side of the base plate the white piston plunger can be seen with a wire-formed connecting rod coupling it to the white crank arm of the servo motor. The aperture plate is polished stainless steel with a 29mm diameter opening.](image)

One end of the housing provides a stable mounting for the servo motor and the PTFE plunger rod. The rod is connected by linkage to the crank arm of the servo motor. The opposite end of the housing contains a cavity for the pressure sensor. The sensor is in direct communication with the vessel fluid. Mineral oil was chosen for its stability, lack of toxicity, and easy handling. It has a different acoustic propagation velocity than the body; however this does not affect the measurement accuracy of structures observed in tissue. Because the acoustic velocity is slower in oil, the vessel appears slightly thicker in the B-mode display than its actual dimension. This does not impact the apparent dimension of anatomical features, as the in-vivo acoustic velocities are unaffected.

The vessel assembly was custom moulded from two part silicone rubber. The diaphragm face is formed to a 0.25mm thickness to minimize displacement backpressure. The remaining faces of the diaphragm assembly are 0.5mm for ease of handling and durability. One face of the chamber has a silicone tube bonded in place to allow a leak-proof bond to the pressure sensor. The pressure sensors were silicon piezoresistive-bridge types tested and calibrated with mineral oil.

The vessel chamber dimensions were chosen to accommodate several constraining factors. The creation of a pump system required a working volume that could be mechanically distorted without the pump plunger or vessel distortions obstructing the ultrasound view. Likewise, the pressure sensor
coupling required space on the opposite end. The centre region was preserved for the observation window created by the aperture plate and the open face of the pressure vessel (the diaphragm). The combination of these dimensional constraints with the need for a simple implementation determines the length of the device from plunger to pressure sensor.

The diaphragm operates most efficiently when it is in a neutral, relaxed state, as it introduces no pressure signal when the diaphragm is flaccid. However it must be capable of substantial displacement in order to modulate local tissue pressure. Figure 3-14 shows the diaphragm in the flaccid, partially extended and fully extended states. In operation the displacement profile is not hemispherical when it conforms to the tissue interface.

Figure 3-14 TSVPP Pressure diaphragm at three states of extension. A) Fully retracted piston (on the right) causes the aperture diaphragm to fully relax. Wrinkles on the surface indicate the existence of an extension range free from diaphragm tension. B) Partially extended piston and diaphragm. C) Fully extended piston and diaphragm.

The width of the chamber was maximized to allow for a large circular aperture without making the device too wide for an operator’s hand. The height of the fluid vessel and chamber is sufficient to accommodate the pressure sensor that is inserted on one face of it. The height has the benefit of
introducing stand-off between the transducer head and the superficial veins. This places the veins closer to the optimal ultrasound focus-depth and improves their rendered accuracy on-screen [123].

**Pump design**

The pump is a positive displacement type that employs a sliding plunger that is mounted on a bearing at one end of the chamber housing. The plunger has a contoured, rectangular piston that displaces the end of the fluid vessel and forces the displacement of the diaphragm assembly. The driven end of the plunger is connected by a link rod to the servo motor. The instantaneous pump displacement is under the control of the microprocessor and can be varied according to the program or by direct user commands. The working range of the pump-diaphragm system is determined by limitations of the system geometry and must be sufficient to achieve the target pressure while accommodating the supporting tissue’s displacement. This displacement is assumed to be small, but non-zero. A peak working pressure of 140mmHg was selected to exceed a calculated maximum lower-extremity haemostatic pressure of 123mmHg for the 95th percentile height of the US male [124] in static standing position. The vessel pressure measurement system is designed to accommodate the over-pressure and under pressure levels concomitant with the pump capability.

The vessel is bounded on all sides by the rigid faces of the chamber, except for the moveable plunger and the circular aperture on the bottom face. Liquid is incompressible, thus the displacement of the working aperture on the face of the chamber is equal to the displacement at the pump face of the chamber. The maximum displacement of the liquid is determined by the plunger area and stroke length. The stroke is limited by the cam rotation angle, set in the control firmware to +/- 70degrees.
Figure 3-15 Schematic of the pump, vessel, and diaphragm displacements. (a) The pump piston is retracted and the diaphragm is relaxed. (b) The pump has been extended and the diaphragm has extended. All but the aperture and the piston faces of the vessel are rigidly bound. The displacement volume at the aperture faces is equal to the displacement volume at the piston face.

The maximum possible volume displacement ‘$D$’ follows Equation 3-1:

\[ D = w \times h \times 2r_c \sin(\theta) = 3380 \text{mm}^3 \]

Where $w$ and $h$ are the width and height of the vessel: 30mm and 8mm respectively, ‘$r_c$’ is the radius from the servo axis to the Link-rod pivot: 7.5mm, and $\theta$ is half the allowed rotation of the servo: $140^\circ$.

The aperture diameter is 29mm; equal to the width of the vessel, less 2mm to ensure control of the diaphragm at the edges. Inside the chamber that constrains the vessel, consideration was given to allow the pump piston to operate without interference. This necessitates clearance between the piston head and the chamber faces. However the silicone rubber walls of the vessel follow the piston movement, creating an effective piston displacement area equal to the cross-section of the vessel.

An initial diaphragm displacement of 2.5 mm at the aperture was chosen as an estimate of the total movement at the tissue interface. This is modelled as a cylinder of uniform height projecting out of the aperture. Though a hemispherical shape is observed when operating the device in free space, placement of the device on body forces the diaphragm to conform to the topology of the anatomy. The
cylindrical projection illustrated in is a simplification used for estimating the adequacy of the system’s displacement capacity.

The maximum uniform-height cylindrical window projection $p$ is described by Equation 3-2:

Equation 3-2

$$ p = \frac{D}{\pi r^2} = 5.1\text{mm} $$

Figure 3-16 Cylindrical model for estimating maximum tissue displacement under the diaphragm. (a) The hemispherical shape only appears when the device is cycled in free air. (b) When the TSVPP is applied to tissue, the displacement shape is limited. For relatively flat locations, the equal volume displacement yields a maximum deflection of $p$.

Where ‘$r$’ is the radius of the aperture: 14.5mm. The calculation indicates that the design intent will be met with margin to compensate for tolerance errors, the variability of the ultrasound probe seating position, and mechanical compliance in the servo-motor linkage.

**Servo motor requirements**

The maximum displacement, surface area, pressure, and sampling rate, determine the motor parameters that are sufficient to support the design targets. These are used to set the minimum torque and velocity requirements for the motor. The pressure ramp waveform used to drive the pump is a triangle wave, but the bell crank mechanism that connects the servo to the piston couples the linear displacement to a cosine shaped displacement from $-70^\circ$ to $+70^\circ$. The peak torque specification on the servo must exceed the pressure-area product of the diaphragm times the lever arm length. Torque on the servo axis is the product of the force * crank radius* sin($\varphi$). Peak torque occurs at $90^\circ$, thus the sine term can be replaced by 1.

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Figure 3-17 Torque calculations for servo motor (all dimensions in mm). The peak torque requirement sets the scale of the pump servo motor.

The simplified maximum torque calculation is the product of the chamber cross sectional area, peak chamber pressure and moment arm length as written in Equation 3-3:

Equation 3-3

\[ \tau = pwhr = 0.34\text{kg} \cdot \text{cm} \]

Where ‘\( p \)’ the vessel pressure, 140mmHg, and ‘\( r \)’ is the bell-crank radius, 7.5mm: ‘\( w \)’ and ‘\( h \)’ are the vessel width and height facing the drive piston. The selected servo is rated at 3kg-cm and allows a factor of 8 margin beyond maximum load for robust operation. The servo velocity is rated at 0.16 seconds for 60° of arc. This allows the full cycle rotation of 280° to occur within 0.75 seconds, ensuring that the 1 Hz sampling rate requirement is achieved.

The materials, methods, and design choices of the TSVPP assembly were constrained by the need to adapt existing and available equipment. The ultrasonic scanner in particular defined many parameters and the final assembly is very specific to the GE Logiq-e instrument. The method and principles though can be generalized and more adaptable and economical implementations of this mechanism can be conceived.

3.3.3 System Electronic Design

The electronics system amplifies and digitizes the pressure signal, generates control signals for the servo motor, accepts commands from the operator and communicates status and pressure data to a local computer. To reduce the possibility of electronic noise entering the data stream, the sensor signal is attenuated by a 30Hz Low-Pass and Anti-Alias filter. It is then amplified and digitized as near as practical to the pressure sensor. The input and servo control lines run in separate shielded
cables to minimize cross talk. The circuit board contains an Analog Devices AD627 instrumentation amplifier, precision voltage references, and the Silicon Labs C8051F320 microcontroller. The latter transmits the digitized pressure values as a serial data stream to the external computer via USB interface.

![Electronics System Functional Block Diagram](image)

Figure 3-18 Electronics system functional block diagram. The pressure sensor is filtered and buffered prior to A/D conversion within the microcontroller. On chip USB peripherals are programmed to transport the digitized data stream to the host computer whilst commands from the user interface are converted into appropriate PWM signals for the servo module, driving the pump. Precision voltage reference supplies drive the sensor and the reference node of the A/D for optimum accuracy and power-supply rejection performance.

Four command switches are mounted on the electronics housing: Mode, Increase, Decrease and Reset. These provide all the required user input to the system in operation. Data are streamed via USB link to the host computer at 15 samples/s.
Figure 3-19 TSVPP Control Circuit Schematic. The use of LM4050 precision references improves sensor and conversion accuracy and repeatability. The highly integrated microcontroller obviated the need for USB peripheral devices.

The schematic for the TSVPP control hardware is shown in
Figure 3-19. The output impedance of the piezo-resistive pressure sensor bridge (not shown) in combination with C2 forms a low-pass, anti-alias filter. AD627 amplifier module provides gain and drive for the A/D convertor integrated into the C8051F320 microprocessor. Four switches are conditioned by de-bounce circuits and provide reset and user commands to the processor. Linear voltage regulators U7 and U3 source the microprocessor (3.3V) and the servo motor (5.0V) separately, while providing supply isolation between the circuits. Precision LM4050 voltage references U6, U4, and U5 source the instrumentation amplifier, A/D external reference, and pressure-sensor respectively.

The circuit design was implemented on a two layer PCB assembly that included switches and indicators. It was sized to mount on the large face of the TSVPP housing.

Figure 3-20 PCB assembly: component layer layout. The board was designed to mount onto the TSVPP housing and allow single handed control of the logic functions while positioning the ultrasound probe. Ultrasound gel contamination problems forced the relocation of the physical board to a sealed housing in-line between the TSVPP probe and the host PC.

3.3.4 Pressure Sensor and Sensor Calibration

Fundamental to the accuracy of the TSVPP is a true representation of the fluid vessel’s internal pressure. This is achieved with a Honeywell type 26PCB piezoresistive bridge pressure sensor. The
sensor is rated for 5PSI and 10V excitation. It provides 10mV/PSI when driven at the rated excitation. Since the sensor is inserted into the mineral oil fluid vessel, calibration studies were conducted using mineral oil as the coupling medium.

A vacuum treatment was employed to extract any trapped air in the sensors, and the system was sealed. On first generation prototypes, a positive pressure chamber was constructed that housed the oil filled pressure vessel assembly. The pressure sensor was coupled through the housing wall to the constrained pressure vessel. The housing was then pumped to a positive pressure using a precision regulator. The internal housing pressure communicated directly to the compliant silicone pressure vessel, and the magnitude of the applied pressure was observed using the Druck pressure calibrator. Leaving the body of the Honeywell pressure sensor outside the housing ensured ambient pressure reached its reference port on the exposed backside of the sensor.

On second and third generation prototypes, a larger pressure vessel was constructed necessitating a new test configuration. Using the same precision pressure calibrator to control the reference port pressure, the differential property of the sensors was then leveraged by applying a controlled and measured vacuum to the reference port of the sensor housing. These pressure differences were
observed from the Druck pressure calibrator while the sensor was connected to the TSVPP system. Differential pressures from the Druck instrument and A/D conversion values from the TSVPP software were recorded into a spreadsheet. This was repeated with 4 combinations of sensor and vessel. Combined response data are shown in Figure 3-22. Because the individual sensors are very linear and closely matched, the fitting equation has a high R2 value. Subsequently, only one equation was used to inform the A/D conversion software in the PC application. Although several sensor and vessels subassemblies were created to support these studies, the durability of the final design resulted in only one pressure sensor & vessel being utilized for all the data acquisition presented in this thesis.

![Sensors Calibration Data: Sets 1-4](image)

Figure 3-22 Pressure sensor calibration data. Highly repeatable sensor responses allowed the TSVPP to use one calibration constant across multiple sensors with negligible effect on accuracy.

### 3.3.5 System Software

To implement this measurement system, several software packages operate concurrently. These include custom PC-software for the data readout, commercial software for the video capture card, frame grabber software for the pc screen, application software of the ultrasound scanner, and the firmware that operates the microprocessor. Figure 3-23 illustrates the flow of information through the
branches of the TSVPP system. The real time vascular images from the Ultrasound scanner are digitized and sent to a host computer. The user commands are sent to the servo motor and echoed in the host computer display screen. The pressure signals from the fluid vessel are digitized by the microprocessor and sent to the display screen of the host computer. The recording computer captures all these data in a single video stream for post analysis. The two custom software implementations required for this system are the PC interface software and the microprocessor firmware.

Figure 3-23 Signal and data flow through the TSVPP system. Morphology data was collected in SVGA video stream and ported through a commercial video capture card. Operator commands and pressure data were routed through the TSVPP electronics board and coupled to the data capture computer using a USB data link.
The microprocessor runs custom firmware to generate PWM signals for the Servo and sample the output of the internal A/D convertor that reads the vessel pressure. These signals, one a displacement command, the other a pressure response, have a non-linear relationship that is dependent on the test environment. For example: if the servo is cycled without the diaphragm being applied to tissue, the maximum pressure achieved will be small. However, with the diaphragm pressed against a limb, the pressure will rise significantly, and can achieve 140 mmHg in normal use conditions. Figure 3-24 illustrates the non-linear relationship between the servo motor PWM signal and the observed pressure. In the data example of Figure 3-24, the TSVPP is applied to a surface that constrains the outward deformation of the vessel diaphragm, resulting in the pressure peak of approximately 50mmHg.

The firmware functions are depicted in Figure 3-25. The firmware allows the user to select either commanded pump displacement or one of three continuously ramped displacement rates. A laptop computer is configured with custom software (called Data Panel) to read data from the USB link and present these on the screen.
Figure 3-25 Microprocessor firmware initialization and execution functions. Start-up routines set the initial position of the pump assembly at a minimum displacement in a static mode. Pressure conversions run continuously. Command switch inputs interrupt the pulse width control routines to change between static values and the three rates of automatic pressure cycling.

Figure 3-26 Non-Invasive Time-Sampled Venous Pressure Probe Computer Interface Panel. Radio buttons on the left reflect the command states set by the user input switches. The pressure bar graph and A/D counts graph reflect the instantaneous chamber pressure. The user can select to write successive pressure readings to a text file.

Figure 3-26 illustrates the visual interface of the TSVPP data panel. The bar graphs and numeric values indicate the A/D counts, pressure, and PWM period. Radio buttons indicate the PWM ramp rate, and the streaming data can be saved in a designated CSV file for later analysis. The software runs on a laptop within Windows and was written in Microsoft C#. The data panel application includes USB initialization and communication functions. The application provides a convenient
human interface to display the information within the microprocessor. Figure 3-27 illustrates the major functions and the process flow of the TSVPP host application software.

The ultrasound scanner screen is captured using the Epiphan video capture card, and the manufacturer’s software is used to present it on the laptop screen. Finally, with the Test Panel application displaying instantaneous pressure data and the adjacent video capture window displaying concomitant ultrasound video, a screen capture tool is used to blend and store the records of vascular activity, pressure and time as a video file. This file is then reviewed post-capture to identify the vein transitions from opened to closed and the concomitant instantaneous chamber pressures that are associated with the transitions. Figure 3-28 shows a screenshot of the Data Panel application adjacent to the real-time ultrasound image of the vein. The Date and time are visible to the hundredth of a second in the Data Panel window. This aids data review. The top right of the ultrasound screen contains the configuration parameters of the Logiq-e scanner. The scale markings between the left
image and the configuration parameters box indicate distance in cm. These can be used to measure vein diameters.

![Ultrasound Image and Configuration Parameters](image)

**Figure 3-28** Shot of Test Panel and Ultrasound Capture Data. Each element of the panel displays one or more clock values to aid synchronizing the data.

The software scheme at this stage of the device development provides data sufficient to determine the utility of this concept without inordinate efforts to create custom code in advance of system understanding. Implementation concepts have been conceived with much greater system integration and automaticity, however their descriptions are outside the scope of this chapter.
3.4 Bench Testing of the TSVPP

3.4.1 Bench Test Model

An initial evaluation of the TSVPP system has been conducted using synthetic analogues for tissue and vein structures. This evaluation work produced insights regarding optimal technique and helped characterize the responses of observed systems.

Vein models were constructed by casting silicone rubber over PTFE forms of various diameters. Once cured, the silicone veins were slid off the forms and imaged to determine the wall thicknesses. These ranged between 0.3 and 0.6mm. Walls were not entirely uniform, but were sufficiently thin and supple such that they easily collapsed in the absence of internal pressure to restore their cylindrical form. These vein models were cast in 5, 6.4, and 11 mm diameters. The vein models were joined to standard plastic laboratory tubing to communicate fluid at pressure into their interiors.

Figure 3-29 Cross section of 11mm silicone 'vein'. Minimal wall thicknesses were targeted to minimize structural effects on the collapsing pressure of filled vessels.

The density and hardness of tissue below superficial veins can range from subcutaneous adipose tissue to bone; from compliant to rigid. In order to observe the effects these extremes might have on the measurement system, two readily available analogues were secured. The first was aluminium block about 3 cm thick, the second was a segment of saturated sponge. No effort was spent considering the hardness match of aluminium to bone, as this was meant only to be an approximation.
to an extreme. However, soft tissue in the forearm and lower leg was tested for “Shore A” Durometer hardness and was compared to the saturated sponge model. Durometer is a measure of the indentation response of a material to a calibrated force. The Shore A scale is used for soft materials having hardness in the range of rubber bands or chewing gum. Though these data represent a small sample, the Durometer values indicate that the two substrates are more alike than different, and thus suitable for a range-finding experiment on the bench. The data are summarized in Table 3-2.

![Shore A hardness measurement of soft tissue. The gage employs a small pin that deflects the target material.](image1)

**Table 3-2 Shore A Durometer readings from various tissue locations. Seven measures were averaged for each entry.**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Superior aspect wrist</th>
<th>Foot, dorsal</th>
<th>Foot medial</th>
<th>Saturated Sponge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shore A Hardness: 7 point averages</td>
<td>4.0</td>
<td>2.5</td>
<td>6.6</td>
<td>3.0</td>
</tr>
</tbody>
</table>

![Rigid and Compliant substrates with simulated vein. The saturated synthetic sponge material was similarly compliant to tissue as indicated by Shore A durometer measurements. The ‘vein’ analogue was secured to the sponge substrate with a small amount of silicone adhesive.](image2)
The bench evaluation required only static pressures that were selectable and well-controlled. The controlled pressures were achieved with a simple gravity feed system. Water was the medium, and the height of the water column was recorded and converted into the corresponding hydrostatic pressure value.

Figure 3-32 Bench test setup with hydrostatic pressure source One objective was to estimate the impact of soft and hard substrates on the accuracy of the TSVPP readings.

The test strategy was to operate the instrument across a range of physiologically relevant pressures whilst observing the ‘vein’ deflection images as the instrument pressure approached, crossed, and departed the equilibrium state with the applied membrane pressure. This was repeated with the rigid and soft substrates, and it was repeated with firm and light operator down-forces used to hold the instrument against the vein and substrate. This latter point is relevant to the extent that operator handling might impact the observation of pressure equilibrium. Two diameters of simulated veins were evaluated, 11mm and 5mm. The bulk of readings were taken using the 5mm vessel model, as it corresponds more closely with the dimension of available peripheral veins in the lower limb.

3.4.2 Bench Testing Results
Figure 3-33 illustrates the response of an 11mm simulated vein in the test fixture at three discrete pressure differences. All three images are taken in the longitudinal orientation. The substrate under the ‘vein’ is compliant saturated sponge, approximately analogous to soft tissue. The operator is applying only light down-force to maintain the instrument in contact with the vein model.

![Image of ultrasound images showing the vein response to chamber pressure. From left to right: low vessel pressure, equilibrium, and over pressure responses are shown. Images are obtained using a linear array probe that produces a planar view. The image plane is perpendicular to the substrate and co-linear with the long axis of the vein. Thus each image shows a ‘slice’ through the long axis of the simulated vein, extending left to right. The substrate is below it, and the observation port and diaphragm interface are about ¼ way down from the top of the image. The diaphragm has an active area extending about 2/3 across the window. The thick, bright horizontal bar on the left edge is a reflection from the stainless steel aperture plate.](image)

The left image has poor contrast at the vein diaphragm interface; however the detail is sufficient to observe the vein bulging upward into the volume of the fluid vessel chamber. A parallel dashed line has been superimposed for clarity. The centre image illustrates a point very near equilibrium, and a slight inward deflection of the vein wall is evident. Also evident in this image are shallow undulations in the membrane near the edges of the observation window. These indicate the laxity of the membrane near its neutral extension position. The right image shows an obvious inward distortion of the vein wall. Notably, the chamber pressure difference between the centre image and the right images is 7mmHg. As the applied vein pressure is 74mmHg, it appears that pressure accuracy may approach 10% with this physical configuration and careful observation.
Figure 3-34 Model ‘vein’ deflections with firm down-force applied between the instrument and the substrate. 74mmHg intra-lumen pressure with 77mmHg and 80mmHg chamber pressures in the left and right images respectively. (The right image contrast has been adjusted to help visualize the upper vein wall.)

Figure 3-34 depicts the same configuration as Figure 3-33. Only the down-force holding the instrument onto the surface of the substrate has been changed from light to firm. The clarity of the membrane-‘vein’ interface is enhanced and the vessel has flattened. The top surface of the vessel wall can be seen to bulge slightly upward in the left image, indicating a slight positive pressure delta. The right image shows a nearly parallel top surface. The equilibrium pressure value for the low down force example appears to be 73mmHg and the equilibrium pressure for the firm down force appears nearer to 80mmHg.
Figure 3-35 depicts the same configuration of the 11mm vein model as Figure 3-34. The orientation of the vessel has been changed from longitudinal to cross-sectional. Here again, 74mmHg pressure inflates the vein. Paying attention to the top surface of the vessel wall, the top left image shows a convex vessel shape. Proceeding from the top left image down the column, the membrane pressure increases. At the 73.4mmHg chamber pressure, the top surface appears planar for the first time. Little discernible change occurs as the diaphragm pressure increases until 80.4mmHg, where the vessel wall begins to appear concave. This is clear at 82.4 mmHg.
Figure 3-36 Six Cross-Sectional views of a vein model with 18.4mmHg intra-lumen pressure as the chamber pressure varies. Firm down-force was applied between the instrument and a compliant substrate. Lumen pressure is 18.4mmHg. Top row, left to right, 4.0, 16.2, and 18.3mmHg chamber pressure. Bottom row: left to right, 19.5, 20.2, and 21.6mmHg chamber pressure.

Figure 3-36 is a sequence of images of a 5mm vein model bonded to a compliant substrate. The sequence shows the vein morphology changes as the instrument cycles from a low applied diaphragm pressure to a higher applied pressure. This vein model was bonded with medical adhesive on the underside to stabilize it onto the compliant substrate. Some of that adhesive creates visual artefacts as described within the image panels. In this test configuration, the applied pressure is 18.4mmHg and the substrate is compliant. The down-force is firm for all the images.

The three images in the top row of Figure 3-36, from left to right, show the vein with three levels of pressure applied by the membrane, 4.0, 16.2, and 18.3mmHg. The flattening of the vessel’s upper wall can be observed in the latter image where the vein-vessel pressure difference is -0.1mmHg from equilibrium. The bottom row first shows another virtual equilibrium and then two successive ‘cusp’ formations in the vessel wall resulting from diaphragm displacement interacting with the adhesive stabilized left wall of the vein model.
Figure 3-37 Six Cross-Sectional views of a vein model over a rigid substrate. 18.4mmHg intra-lumen pressure is applied as the diaphragm pressure. Firm down-force was applied between the instrument and the rigid substrate.

Figure 3-37 is a sequence of images of a 5mm vein model bonded to a rigid substrate to simulate bone. The applied intra-venous pressure is 18.4mmHg. The down-force is firm for all the images. A sequence screen captures records the morphology changes as the instrument cycles from a low applied pressure to a higher applied pressure. This vein model was also bonded with medical adhesive to stabilize it onto the rigid substrate to simulate bone. Again, some of that adhesive creates visual artefacts as described within the image panels. Additionally, reflection artefacts below the image of the vein appear more intensely in the ‘rigid substrate’ region of the b-mode image at the level of 2.0-2.5cm. This is most apparent in the top-left image of Figure 3-37.

The three images in the top row of Figure 3-37, from left to right, show the vein in various states of pressure-balance with the membrane. The top left image shows the vein model nearly fully expanded as the membrane pressure is 11.1mmHg less that the vein pressure. The central image
displays a convex upper ‘vein’ wall with a membrane pressure 1.4mmHg less than the vein. The top right and bottom left images show a substantially flat-topped wall with 0.4mmHg under-pressure and 0.3mmHg overpressure respectively. The bottom centre and bottom right images demonstrate a concave upper wall that transitions to a collapsed ‘vein’ structure with 2.4mmHg and 3.4mmHg overpressure respectively.

Table 3-3 Summary of applied lumen pressures, estimated lumen pressures and test conditions

<table>
<thead>
<tr>
<th>Lumen Pressure mmHg</th>
<th>Low Estimate</th>
<th>Best Estimate</th>
<th>High Estimate</th>
<th>Lumen Diameter</th>
<th>Substrate Material</th>
<th>Orientation</th>
<th>Down-force</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>---</td>
<td>73</td>
<td>---</td>
<td>11</td>
<td>Sponge</td>
<td>Long</td>
<td>Light</td>
</tr>
<tr>
<td>74</td>
<td>---</td>
<td>80</td>
<td>---</td>
<td>11</td>
<td>Sponge</td>
<td>Long</td>
<td>Firm</td>
</tr>
<tr>
<td>74</td>
<td>69</td>
<td>73</td>
<td>80</td>
<td>11</td>
<td>Sponge</td>
<td>Cross</td>
<td>Firm</td>
</tr>
<tr>
<td>18.4</td>
<td>16</td>
<td>18</td>
<td>20</td>
<td>5</td>
<td>Sponge</td>
<td>Cross</td>
<td>Firm</td>
</tr>
<tr>
<td>18.4</td>
<td>17</td>
<td>18</td>
<td>21</td>
<td>5</td>
<td>Aluminium</td>
<td>Cross</td>
<td>Firm</td>
</tr>
</tbody>
</table>

Table 3-3 summarizes the image and pressure data. Little difference in estimated pressure is observed between Longitudinal and Cross-sectional orientations of the 11mm vessel. Likewise little difference is seen between the estimated pressures for the 5mm vessel on aluminium and sponge. These results are typical behaviour of the system on the test bench.

3.5 Analysis and Discussion

The structure of the bench measurements was created to allow for the evaluation of the gross characteristics of the TSVPP in use, and to discover potentially unanticipated relationships about the functionality of the design and the relationships between the design and the test environment. In this study, a simulated environment was created with silicone tubes for veins, sponge for tissue, and a metal plate for bone. Several questions motivated the bench exercise: Was the hardware and firmware truly functional? Would cross sectional or longitudinal views be more effective? How should the device be handled for best results? What would be the effect, if any, of a vein resting on bone compared to a vein resting on adipose or muscle tissue? What would a vein look like at pressure equilibrium? How much pressure change would be observed between the start of a venous morphology response and the eventual closure of the vein?

The hardware, software, and electronics worked well together and provided generally acceptable performance. Modifications were made to the electronics location, moving the circuits to a separate
housing to protect the assembly from the contamination by ultrasound gel. An observation of measurements taken with light and firm down-forces indicated that firm down-force on the model allowed the pressure of the vessel to equilibrate to the pressure of the chamber at lower diaphragm extension distances. This effectively reduces the outward curvature of the diaphragm and minimizes the pressure error associated with displacing the diaphragm beyond the neutral plane (displacement pressure error). Further reductions of displacement pressure error effects were achieved by pre-stretching the diaphragm during the build process and bonding it around the perimeter in a pre-tensioned state. This created an operating range of negligible pressure displacement that extended 1-2mm above and below the neutral plane.

The obvious orientations for vein imaging are longitudinal and cross sectional views of the structure. Views at intermediate angles were not considered. Longitudinal views were informative and instructive for the bench evaluations. The large image of the vein eases the task of identifying the equilibrium point. However the complex pathways of anatomical veins do not often provide accessible, straight vessel segments that are suited to this view. Thus the cross-sectional views appear most appropriate for study and for practical extensibility to in-vivo applications.

Centralization of the vein image in the ultrasound’s field of view is both intuitive while using the imager and desirable to enable optimal system accuracy. Diaphragm mobility at the edges of the aperture is inhibited relative to the central region, and the ultrasound imaging is limited to the regions within the aperture. Subsequently, the best pressure coupling, accuracy, and visual resolution are found when the vein is cantered under the diaphragm aperture and the vein image is centred in the ultrasound display screen.

The use of compliant and rigid substrates was employed to evaluate for the possibility of gross interactions between the measurement response and the alternate possibilities of bone or adipose/muscle tissue underlying veins of interest. There was no apparent impact on the measurements taken on vein models at 18mmHg. However the image quality deteriorated somewhat from reflections from the aluminium plate acting as the bone model.

The definition of pressure equilibrium was when the measured sensor pressure equalled the hydrostatic pressure, which was easily calculated in the simple setup. In these data, the equilibrium
appeared to be the configuration where the vein wall nearest the pressure diaphragm lost its convex shape from positive internal pressure and flattened. Where the vein wall transitioned to convex under pressure from the diaphragm was considered to be the overpressure event. This definition was obtained in a system created with finitely-thick silicone tubing for veins and these differ markedly from the reality of living tissue. The silicone veins had substantial asymmetry and in some cases were bonded at the sides to enable testing. These factors alone can and may have confounded some of the results. However, as a bench evaluation, they provided substantial utility.

Though this evaluation work was not blinded or statistical, the general accuracy that was realized in the bench testing was about +/- 10%. This result indicates a good potential for in-vivo utility. The analogues of veins and tissue were simple in the extreme; however the data suggest that cross-sectional views with firm holding pressure are a worthwhile starting technique for anticipated non-invasive in vivo studies.
Chapter 4

*In-Vivo* Evaluations and Results
4.0 Introduction

In Chapter 3, the Non-invasive Time-sampled Venous Pressure Probe (TSVPP) design was described, and a prototype of the system was tested and characterised in vitro. The initial results from in-vitro testing indicated the TSVPP had the potential to accurately represent hydrostatic pressure with an error factor approaching +/-10% of the true value. The impact of variable tissue-density underlying the veins was simulated with physical models, and it was determined to have no observable impact on the measurement system. Valuable experience was gained in the use of the TSVPP under simulated conditions, and the hardware and software demonstrated sufficient capability and stability to justify continued study under more realistic and challenging conditions. In this chapter, the methods and results from in-vivo TSVPP testing using Ovine and Canine foreleg models are presented. The purpose of in-vivo testing was to determine the optimal method for identifying the venous morphology associated with pressure equality between the TSVPP reading and vein lumen. Other objectives were to obtain reliable reference pressure reference data with which to evaluate accuracy of in-vivo TSVPP measurements, observe the TSVPP device interactions with an intact, functioning vascular system and identify device and study limitations. The study objectives are summarized in Table 4-1.

<table>
<thead>
<tr>
<th>Primary study objectives</th>
<th>Conditions and effects 1</th>
<th>Conditions and effects 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify venous morphology of pressure equality using reliable intravenous pressure reference</td>
<td>Low, medium and high venous pressures</td>
<td>Slow and fast sampling rates</td>
</tr>
<tr>
<td>Observer TSVPP interactions with the venous system</td>
<td>Diaphragm extension effects</td>
<td>TSVPP application effects</td>
</tr>
<tr>
<td>Identify Device and Study limitations.</td>
<td>Pressure modulation approach</td>
<td>Animal model discrepancies to human application</td>
</tr>
</tbody>
</table>
4.1 Methods

As discussed in Chapter 2, the primary factors that influence peripheral venous pressure can be classified into static and dynamic categories. The design of these \textit{in-vivo} experiments was limited by institutional and ethical requirements for fully-anesthetized animal models, (Elaborated in section 4.1.1.) Therefore, the dynamic influences of skeletal muscle activity and postural changes concomitant with ambulation were out-of-scope for current testing. The significant factors that could influence peripheral venous pressures were substantially static within the time-frame of the experiments. These included capillary-bed resistance, venous resistance, and arterial pressure. A means of introducing controlled-venous-hypertension was required, and the approach selected was the use of a pneumatic blood pressure cuff applied to the limb under test. This allowed the study to evaluate arbitrarily elevated venous pressures in a controlled manner, up to the limit of the systolic blood pressure. The effect of a limb pressure cuff is illustrated in Figure 4-1. Using this effect, the venous pressure in the animal models was effectively controlled by an artificial venous resistance, furnished by the proximal limb-pressure cuff.

![Diagram of limb cuff effects on venous pressure](image)

Figure 4-1 A simplified view of limb cuff effects on venous pressure. a) Cuff pressure less than venous pressure: The proximal and distal pressures adjacent to the cuff are unaffected. b) Cuff pressure pumped above venous pressure: Distal venous pressure begins to rise with arterial filling until venous pressure equilibrium with the cuff. c) Cuff pres-
sure pumped above arterial pressure: The cuff closes all flow. Arterial pressure falls, and venous pressure rises to a common equilibrium pressure less than the systolic pulse pressure of the artery. Secondary factors that modulate the venous pressure include Positive End Expiratory Pressure from the ventilator and the vertical distance between the cannula tip and the right atrium. These secondary factors were controlled or monitored during the setup of the studies. Physiological parameters such as capillary-bed resistance and venous resistance were overwhelmed by the external circulatory modulations of the experimental setup, and they are not considered to have any significant pressure impact. One factor that can modify the observed reference pressure, but does not alter the true venous pressure, is the vertical offset between the cannula tip and the height of the reference pressure sensor. This offset was carefully measured and minimized during the setup phase of each experiment. Figure 4-2 illustrates the factors that influence the venous pressure and the reference pressure values. It also depicts the means employed for observing and recording those data.

Figure 4-2 *In-vivo* pressure modulation factors and signal flow. a.) System under test. b.) TSVPP detection and recording system. c.) Intravenous cannula. d.) Height offset from cannula needle to reference pressure sensor. e.) Reference pressure recording system.
The experimental setup of Figure 4-3 was constructed to fulfil the objective of comparing indirect pressure correlation data from the TSVPP and direct cannula manometer readings across a range of experimenter-controlled venous pressures. In addition to providing a reliable reference pressure value, the direct cannula pressure record allowed for the observation of TSVPP effects on the venous system.

![In-Vivo Pressure Measurement Configuration](image)

**Figure 4-3 In-Vivo Pressure Measurement Configuration.** Saline flush is used to obtain hydraulic continuity between the pressure sensor and the cannula tip. The vertical heights of the sensor and cannula tip are matched to reduce hydrostatic offsets.

### 4.1.1 Ethics

The conduct of these studies was approved following a review process by the Institutional Animal Care and Use Committee (IACUC) of Boston Scientific. The authorization required the evaluations to be conducted as tag-on studies: i.e. the studies were conducted on animal models that immediately
prior to testing, had been used for primary, unrelated, non-surviving studies. This is consistent with the objective of maximum utilization for all animal models. Thus the condition of the animals available for evaluation was variable and depended to some degree on the impact of the prior studies.

The IACUC review process established animal use justification based on the following criteria

- This study does not duplicate prior Boston Scientific controlled investigations.
- This study does not duplicate any other previous studies based on the Literature Search findings
- The current state of scientific knowledge does not provide acceptable alternatives (e.g. in vitro) to the use of live animals in this study, thus a preclinical investigation is necessary.
- Physiological conditions are needed for the accurate testing of venous pressures.

The protocol approval authorizing the conduct of these studies allowed the use of Swine, Ovine and Canine models.

4.1.2 Animal Care & Anaesthesia

Animal management and care was approved by IACUC and supervised by a veterinarian to ensure appropriate and humane treatment. Animals were fasted overnight prior to acute procedures. Due to the variety of species, mass, and primary procedure requirements, anaesthesia and homeostatic maintenance varied between studies. Either of Telazol, morphine, or Butorphanol was administered for sedation, and intravenous Propofol was administered prior to intubation. Lactated Ringers Solution was delivered intravenously for maintenance of fluids. Loading doses of morphine and ketamine were administered for analgesia with constant rate of infusion of each. Phenylephrine was used to support blood pressure as needed, and lidocaine was employed to attenuate cardiac arrhythmia. Animals were oriented on right lateral decubitus or left lateral decubitus positions on a horizontal surgical table.

Prior to euthanasia, 5% Isoflurane was delivered from a positive pressure ventilator to induce deep plane of anaesthesia. 20ml KCL (2mEq/ml) delivered intravenously for euthanasia.

4.1.3 Experimental setup
Evaluation of the TSVPP performance was based on observations conducted on superficial veins in the distal regions of the animal’s forelimbs. The cephalic vein of the forelimb was selected. The reference pressure signal of the target vein was obtained via the cannulation of the most distal and accessible region of the cephalic vein. Once the vein site was identified, a 19 gage cannula was inserted, and the reference pressure sensor position was adjusted to ensure that its vertical plane was within 2cm of that of the cannula tip. The reference pressure position relationship is illustrated in Figure 4-3 and is shown directly in Figure 4-5. The pressure sensors were Argon Medical Devices\textsuperscript{1} DTX-Plus TM DT-4812 transducers. These were calibrated immediately prior to use with a VWR\textsuperscript{2} model 3460, NIST traceable pressure calibrator (Figure 4-5). Sensors were coupled to ADInstruments\textsuperscript{3} Power Lab transducer amplifiers, and data were digitized using a PowerLab data acquisition module (AD Instruments PL3516) and recorded using LabChart\textsuperscript{3} Version 7.

\textsuperscript{1} Argon Medical Devices Inc. 5151 Headquarters Drive Suite 210 Plano, TX 75024 USA
\textsuperscript{2} VWR P.O. Box 6660 100 Matsonford Road Radnor, PA 19087-8660
\textsuperscript{3} ADInstruments Ltd Unit B, Bishops Mews, Transport Way Oxford OX4 6HD UNITED KINGDOM
4.1.4 TSVPP Operation and Test Parameters

The measurement of venous pressure using the TSVPP is based upon inducing pressure transitions across the vein-wall with the TSVPP diaphragm as it presses on the tissue superficial to the veins. The pump cycle interval, from minimum to maximum pressure and back, fixes the sampling rate. Sampling rates were selected from Very Slow (23.1s), Slow (4.6s), Fast (1.13s), and Static modes. The Static mode allows the operator to manually find the equilibrium pressure between the TSVPP sensor and the vein. This is done by incrementing the diaphragm pressure on the tissue, whilst observing the B-mode image in real-time. The Very Slow and Static modes are designed to be primarily instrument setup modes because under these settings the interaction between the diaphragm and vein can be observed with a high density of video frames. This allows careful study of venous morphology in various states of pressure equilibrium and imbalance. The Slow and Fast modes are intended for time-sampled physiological measurements, as at these sampling rates observations can be spaced closely in time to enable the reconstruction of the dynamic pressure changes in the vascular system that occur with emptying, refilling, and muscular contractions.

Control of venous pressure

Three venous pressure ranges were obtained by modulating the cuff pressure which allowed for controlled pressure states in the system. Three levels of pressure were employed Low: ≤30mmHg, Medium: ≥ 30mmHg, ≤ 50mmHg, High: > 50mmHg. Low pressure was simply the resting venous pressure with no pressure applied to the cuff. Medium venous pressure was obtained by inflating the
pressure cuff to approximately 50mmHg. High venous pressure was obtained by inflating the pressure cuff between 60 and 120mmHg. This technique caused the venous pressure in the distal portion of the limb to increase to match the cuff pressure. When the pulse pressure exceeded cuff pressure, arterial flow into the limb increased the venous pressure until equilibrium was reached with the cuff. Arterial inflow beyond the equilibrium pressure resulted in venous outflow past the pressure cuff constriction. In this way, venous pressure in the limb could be driven to arbitrary levels, so long as the cuff pressure did not exceed arterial pressure and obstruct flow into the limb.

**Data processing and display**

The data methods selected for this project were chosen to minimize hardware and firmware development time and to obviate the need to modify the internal workings of an expensive clinical ultrasound instrument. However a substantial penalty was paid for this through the requirement for painstaking post-experimental data analysis. Three streams of information were combined, TSVPP pressure data, reference pressure data, and B-Mode video. This required substantial video processing, reference video generation, and synchronization.

Video data were collected from the acquisition computer using Camtasia\textsuperscript{4} Studio Version 8 software and post-processed using Adobe\textsuperscript{5} Premier Elements 11. Video data were reviewed frame-by-frame using VLC\textsuperscript{6} media player Version 2 and Daum\textsuperscript{7} Pot Player Version 1.5. Cannula pressure data collected using AD Instruments Power Lab and Lab Chart software were exported to MATLAB\textsuperscript{8} Version 8.1(R2013a) and processed for display as a motion graphic with Pressure and time on Y and X axes respectively.

The collection and collation of TSVPP pressure observations and instantaneous cannula pressures occurred in post-processing. Pressure equilibrium events in the B-mode images were matched to the corresponding chamber pressure values at the time the video frame was captured. Due to systematic B-Mode video capture delays, video frames were recorded about 300ms after the data were collected. This temporal offset was identified in the post processing analysis phase. Time deltas

\textsuperscript{4} TechSmith Corporation 2405 Woodlake Drive, Okemos, MI 48864-5910 USA  
\textsuperscript{5} Adobe Systems Incorporated 345 Park Avenue, San Jose, CA 95110-2704  
\textsuperscript{6} VideoLAN 18, rue Charcot, 75013 Paris, France  
\textsuperscript{7} Daum Space. 2181 Yeongbyeong-dong Jeju-si, Jeju-d, Korea  
\textsuperscript{8} The MathWorks Ltd. Matrix House, Cowley Park, Cambridge, CB4 0HH UNITED KINGDOM
were made apparent by the temporal dissociation between the record of the chamber-pump drive and the video record of the diaphragm extension. These events would ideally have been recorded on the same video frame for a zero latency system. However, the extensive review of multiple video files established the B-mode delay was nearly constant at 250 – 300ms. Each video segment was assessed for the time-shift before determining the correct offset time. This offset was used to find the video frame with the pressure reading corresponding to the B-mode vein/diaphragm equilibrium observation.

The configuration of the TSVPP data interface has been described in Chapter 3. The version used for the in-vivo testing incorporates an additional graphics panel to display the cannula reference pressure data. Figure 4-6 is an example of the data interface. There are three data regions: The top region is the B-mode ultrasound view; the bottom left region is the TSVPP data window; and the bottom right view is the Reference Pressure window. The lower-left Panel has three status bars, of which the top is the most important. It reports the TSVPP chamber pressure. The lower bars report internal controller values. The radio buttons on the far left indicate the mode of the TSVPP pressure chamber modulations; Off, Stepped (manual), Slow, Fast, and Very Slow rates.

The Reference Pressure Window is unique to the in-vivo evaluations. It presents the reference pressure value obtained from the cannula manometer. The instantaneous pressure is the centre of the graph highlighted with a small box, and the instantaneous pressure is reported numerically at the top right corner of the window. The graph presents the pressure as a function of time, extending 2.5s prior to and subsequent from the instant of observation. The Y-axis of the reference pressure graph auto-scales and displays the full range of pressure values within the 5s window of observation.
4.2 Results

4.2.1 Animal suitability

Of the animal species evaluated, the ovine model was usable, and the canine model was preferred. Table 4-2 summarizes the animal models employed and the observations regarding general suitability for the TSVPP evaluation.

Table 4-2 Animal model suitability for TSVPP evaluation

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Model Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovine</td>
<td>Hind limbs were completely unsuitable for pressure cuff due to their steeply-tapered muscular shape shedding the cuff. Forelimbs accepted the cuff. Relatively short forelimbs were difficult to cannulate whilst leaving access for the TSVPP. Useful data were obtained from forelimb measurements.</td>
</tr>
<tr>
<td>Canine</td>
<td>Hind limbs were unsuitable. Forelimbs accepted the pressure cuff and TSVPP with improved access over other available animal models. Longer forelimbs provided better access and greater vein compliance that was noticeable when the pressure cuff was inflated. (see text)</td>
</tr>
</tbody>
</table>
4.2.2 Ovine TSVPP results

Ovine data was predominately recorded in *Slow* mode to provide a substantial record of high resolution data capturing the pressure equilibrium events between in TSVPP diaphragm and the veins. Short segments of *Fast* and *Very Slow* data were included. The limb cuff pressure was configured to drive medium and high range intravenous pressures, as observed with the cannula manometer. These configurations were emphasized to evaluate the pressure modulation technique and to provide data representative of static standing lower limb venous pressures.

Figure 4-7 shows a representative image of the cephalic vein with a cannula measured internal pressure of approx. 32mmHg while under observation by the TSVPP sensor. In Figure 4-7a, the TSVPP is applying negligible external pressure to the tissue at the instant of image capture. The TSVPP diaphragm can be seen just above the vein. The TSVPP diaphragm is relaxed. The vein, indicated by the arrow has a clearly defined lumen, and visible just below the vein is a shadow of the underlying bone.

Figure 4-7b illustrates the effect of increasing the TSVPP chamber pressure to 32mmHg. This results in the nearly complete closure of the vein, Figure 4-7b was collected just one second after the image in Figure 4-7a. The marked difference in vein morphology appears as the TSVPP diaphragm pressure ramps up to and exceeds the vein lumen pressure.

![Figure 4-7 Cephalic vein pressure data: a) Open vein with 32.7mmHg pressure and negligible external pressure. b) Closed vein with 33.2mmHg internal pressure and 32mmHg external pressure.](image-url)
In the ovine evaluation, the cannula pressure data revealed the presence of cardiac pulse artefacts in the venous lumen. These can be seen in Figure 4-8. The reference pressure window reports the instantaneous lumen pressure as 34.6mmHg, and the graph indicates a nearly sinusoidal pressure undulation with a frequency corresponding to 96 beats per minute. The amplitude of the pulse pressure is about 5mmHg peak to peak over a baseline of about 37mmHg. When the phenomenon could be observed, the pulse amplitude ranged from 2-5 mmHg at mean venous pressures ranging from 20-90mmHg with no apparent dependence on the mean. This was thought to be the result of a closely adjacent artery coupling pressure waves via wall pulsation.

![Figure 4-8 An expanded view of the cannula pressure](image1)

The cannula signal reveals arterial pulse pressure artefacts with an amplitude of 4mmHg. The pressure pulse interval corresponded to 96 bpm and agreed with the surface ECG monitor observations. The artefacts were surprising, but likely due to the close proximity of the vein to the artery under a state of significant external compression from the pressure cuff.

In the course of evaluating the TSVPP using varied degrees of induced venous hypertension, the pressure cuff was inflated from 0mmHg to values in excess of systolic pressures. The cuff was inflated beyond the systolic pressure several times, and a representative image of the resulting pressure state is shown in Figure 4-9. In this figure, the cuff was inflated to a high pressure, and the TSVPP was applied to the superficial vein on the limb. The static venous pressure achieved from the cuff occlusion was 65.2mmHg and is the baseline pressure shown in the plot.
Figure 4-9 An example of cuff-induced high venous pressure

a) The maximum steady state pressure is 65.2 mmHg. All venous outflow and arterial inflow has been blocked, and the TSVPP is applied throughout the interval. b) A large pressure spike occurs during each extension phase of the TSVPP chamber pump cycle because the small vascular volume has been fully occluded.

There is a very large pressure spike at the left side of the plot with the start of another pressure pike on the right side of the plot. The interval is about 4.6 s, corresponding to the chamber pump-cycle interval associated with the Slow mode of data collection. The Slow Ramp radio button is highlighted, as can be seen in the TSVPP control panel on the bottom left of the figure. This TSVPP induced pressure increase is approximately 20 mmHg over the baseline. Figure 4-10 presents an alternate view of the venous pressure over this interval, displayed on the Lab Chart software. The pressure spike intervals and magnitude relative to the baselines are more apparent in this image.

This unusual pressure ramp was apparent during certain experiments when the cuff pressure was quite high and there was no outflow possible from the limb. The pressure ramp occurs when the distension of the TSVPP diaphragm displaces the vein lumen and the venous flow is obstructed. It is not expected system behaviour for normal operation, but it reflects the interaction of the TSVPP
system with the method of induced venous hypertension.

Figure 4-10 A 16 second interval showing cuff-induced elevated venous pressure with TSVPP chamber-cycle mediated pressure spikes. (Lab Chart data display)

Figure 4-11 represents an equivalent test from Canine 2. In this figure, the pressure cuff is deflated, but the TSVPP is applied to the vein in the same manner as Figure 4-8 and Figure 4-9. No pressure surges are apparent from the TSVPP. This is more apparent in Figure 4-12, the Lab Chart view of the same data over a 16s interval.
Figure 4-11 An example of a TSVPP operation on a vein without the cuff occlusion. The TSVPP diaphragm is displacing the vein wall, however no pressure artefact is observed.

Figure 4-12 A 16 second interval showing normal venous pressure with deflated cuff. The TSVPP diaphragm is displacing the vein wall, however no pressure artefact is observed.
Slow-Mode pressure measurements are displayed in Figure 4-13. The dashed line on the plot represents an ideal 1-to-1 correlation between the reference and measured pressures. The raw data points (open symbols) did not correlate well to expected pressures. Further post-processing to correct for B-mode frame-delay was applied to the data set. The post processed data are shown in filled symbols. The correlation is markedly better with the delay-corrected data. Two data points diverge from the population. These ‘outliers’ were excluded for the simplified plot shown in Figure 4-14 which shows the correlation between the TSVPP pressure observations and the reference cannula pressure. The linear fit slope is 1.09 and the correlation coefficient is 97.2%.

![Ovine: Slow Rate Data Points](image)

*Figure 4-13 Compilation of data from Ovine1 study. Open markers indicate vein closure events from raw data. Filled markers indicate time-corrected vein-closure data. The large dashed oval highlights outliers.*
Figure 4-14 Ovine 1 pressure correlations after the video time-correction was applied. Two anomalous points were excluded. (See discussion)

The ovine study was concluded without substantial Static, or Very Slow rate data. These were obtained in the Canine1 and Canine2 studies.
4.2.3 Canine TSVPP results

Two animals were part of the Canine study, Canine1 was limited to data collection using *Very Slow* mode and the corrected time shift data is shown in Figure 4-15. These data were collected from reference pressure conditions ranging from 20 to 58mmHg. The linear fit slope of these data is 0.95 and the correlation is 0.78. This correlation coefficient is markedly less than for Ovine1 data.

![Canine1 Pressure Correlation: Very Slow Mode: n=8](image)

*Figure 4-15 Canine 1 pressure correlation using Very Slow Mode.*

The Canine2 study generated data using *Slow*, *Very Slow* and Static modes of operation. The collection of static pressure data was conducted to clarify the morphology of the vein lumen at interesting states of internal and external pressure. This was achieved by bringing the TSVPP slowly up to the equilibrium pressure and slightly beyond it. The B-mode portion of the data display contains the vein morphology information. The data shown in Figure 4-16 are from the Cephalic vein of Canine2. In all the images of this figure, the data were selected from within a stable interval to diminish the influence of dynamic events to minimize inter-lumen pressure changes. Typically, the preceding 300ms of data are nearly identical. In Figure 4-16a, the cannula reports an internal lumen pressure of 48.6mmHg. This is about 10mmHg greater than the externally applied TSVPP membrane pressure. The lumen is flattened, but distinctly open. Similarly in Figure 4-16b, the vein is only
2.5mmHg over pressure from the membrane, but the lumen is clearly open. Finally Figure 4-16c shows closure of the lumen with about 2 mmHg of TSVPP diaphragm pressure over the lumen pressure.

Figure 4-16 Canine2: Manually controlled steady-state data showing the Cephalic vein cross section: a) Vein-TSVPP≈10mmHg. b) Vein-TSVPP≈3mmHg. c) TSVPP-Vein≈2mmHg.

The plotted Very Slow-mode data of Canine 2 are shown in Figure 4-17. These data were taken across the range of 18 to 100mmHg of venous pressure. The linear fit line is characterized by a slope of 0.98 and a correlation coefficient of 0.98.

Figure 4-17 Canine 2: Time-corrected data taken with Very Slow Mode
*Slow* mode data were obtained over a venous pressure range of 18 to 64mmHg. The data and the linear fit are shown in Figure 4-18. The slope is 1.05 and the correlation 0.94. These data were combined into the plot of Figure 4-19. This figure shows a linear fit slope of 1.01 and a correlation coefficient of 0.96.

![Canine2 Pressure Correlation: Slow Mode: n=11](image)

**Figure 4-18** Canine 2: Time Corrected Data taken with *Slow* Mode.
4.2.4 Impact of device alignment

In Figure 4-15, the Canine 1 Very Slow mode graph, data point (22.7, 35) contributes markedly to the reduction in the fitted-line correlation. Excluding that particular data point from the linear fit results in an $R^2$ value of 0.94 versus the 0.78 with the point included. Alignment analysis was conducted to establish the potential impact of TSVPP device alignment to the observed pressure values.

Figure 4-20 shows a screen capture of the TSVPP pressure diaphragm fully extended into free space. Superimposed on the arc of the diaphragm is an ellipse. The ellipse identifies the central axis of the diaphragm. A 2mm grid is superimposed on the screen referencing the in-built cm scale of the Ultrasound Imager display. The grid index provides a spatial map of the ultrasound imaging plane as it intersects the TSVPP diaphragm.
An image of the Canine1 foreleg is captured in Figure 4-21 that shows the open lumen of the vein nearly aligned to the central axis of the TSVPP diaphragm. The diaphragm is in a relaxed, low-pressure state and is conforming to the topology of the anatomy. The vein outlined in Figure 4-21 nearly centred on the axis of the diaphragm.
Figure 4-21 Canine 1 view of a vein well-aligned to TSVPP diaphragm axes

Figure 4-22 Canine 1 view of a vein poorly-aligned to TSVPP diaphragm axes
The image shown in Figure 4-22 was captured close to the time of the errant data observation, point (22.7, 35). Both the vein lumen and the underlying bone can be observed. Each is substantially shifted to the negative x direction. All the data points associated with Figure 4-15 were analysed for X axis offset and TSVPP observed pressure mismatch. These data are depicted in Figure 4-23. The point of greatest misalignment is the same datum of point (22.7, 35) in Figure.

![Very Slow Mode Pressure Error vs. Misalignment](image)

**Figure 4-23 Plot of X-axis misalignment and pressure error**

Figure 4-24 depicts the *Very Slow* mode data collected from Canine1 with the substantially misaligned data point removed. When compared to the original data set represented in Figure 4-15, the correlation constant is improved from 0.78 to 0.94. The slope diminishes slightly from 0.95 to 0.092. While the slope reduction appears counterintuitive given the specific datum deleted, it is a consequence of the zero intercept assumption used in the line-fit calculation. The significance of removing the off-axis data point is reflected in the improved correlation constant.
Table 4-3 summarizes the data collected from the ovine and canine studies. Though not elaborated with a graphic representation, the fast data collected from the ovine model had very poor correlation to the reference pressure. The remaining modes of operation produced results with acceptable slope and correlation factors.

4.3 Analysis and discussion

The animal models available for these studies were only partially suitable for the intended measurement, due to limitations on species availability and institutional constraints. All the in-vivo
data were collected from short duration “tag-on” studies that utilized available time on animal models that had already served a prior, separate investigation. The continuity of anaesthesia was maintained, but the duration of available study time was short, and the arrangement allowed for no control over specifics like weight and prior conditioning. These constraints on animal models significantly impacted the types of measures that were conducted and limited the number of repeated measures that were possible. However, the scope of the study limitations did not eclipse the value of substantial new information that was realized.

These study objectives were centred on potential human applications for the lower leg and foot in particular. From a dimensional perspective, the venous structures of the models were substantially shorter than those of adult humans. This created the need to modulate venous pressure by measures other than utilizing the hydrostatic pressure changes that occur from human postures of sitting, standing, and from various permutations of angle and height differences. The effective maximum vertical distance available in the animals under anaesthesia was about 0.5m. The distance is short compared to a value of 1.5m more typical in man. Additionally, the use of anaesthesia in the animal models and requirement for a recumbent position on the surgical table limited the available distance to 0.2m or less. These facts drove the use of the pressure cuff method for inducing substantial venous pressures at will.

While the cuff was an effective method in facilitating modulation of pressure, it changed the haemodynamics of the veins under evaluation. In particular, the cuff closed the vein at a location just proximal to the evaluation site. This is indicated in Figure 4-3 and Figure 4-4. This closure isolated the distal vein volume from the remaining circulatory system. The movement of venous blood and the transmission of pressure waves in the ascending venous track to the vena cava and right atrium were removed. Blocking the venous return path has the potential to convert TSVPP diaphragm mediated displacements of the venous wall into very substantial pressure changes within the vein as seen in Figure 4-9 and Figure 4-10. In the intended human applications, this venous return path is open. However, despite the open return path, the TSVPP diaphragm displacement could affect human vein pressure slightly. This would be an undesirable measurement artefact. This was evaluated in low-pressure animal studies where the vein was left unobstructed by the pressure cuff. In these cases,
the modulation of venous pressure was not observed (Figure 4-12). Therefore this effect is not expected to be significant in human use.

The animal model data demonstrate that the veins of the observed limbs reflect a faint cardiac pulse, though a highly sensitive manometer was required to detect it. It is suspected that cross-coupling of arterial pulsations to adjacent veins is the cause of the venous cardiac pulse. These pulsations have been observed throughout much of the data. The magnitude of this cross-coupling was observed to in the range of 0-5mmHg, an order of magnitude less than pulse pressures measured in adults [125, 126]. The amplitude of this coupled pulse appeared to be independent of the steady state venous pressure, except when the cuff was inflated beyond the systolic pressure. In these cases, complete occlusion of the limb vasculature trapped pressure in the veins and arteries, and eliminated the pulse entirely. This latter configuration is not relevant to the intended application of the device, as the cuff was only an investigative tool for this study.

Finally, the presence of a faint pulse waves in the venous system does not present an accuracy problem. In humans, where the target vein will be more superficial and distant from adjacent arteries, no pulse signal is expected. To the degree that it is a natural phenomenon, it is an appropriate part of the instantaneous venous pressure. In the case of an Ambulatory Venous Pressure Measurements, the expected pulse pressure variation is expected to be small compared to the expected range of values: (0-5mmHg, compared to 20-120mmHg)

Time synchronization was a significant problem for the prototype system evaluated here. However, the temporal delay causes were identified and corrected in the data. The dominant cause was the processing delay of the VGA capture device used to record the B-mode video onto the computer running the TSVPP. A secondary cause was dropped video frames arising from the interactions of the video stream and the laptop’s internal processing burdens. In a fully developed system, these delays would be eliminated, or fully characterized, stable, and compensated in the system design.

The results observed with the Fast mode were unusable. The vein closure delay associated with blood’s inertia and venous resistance combined with the system phase delay to obscure the utility of the data. The final data appear fully uncorrelated.
This observation does not automatically drive the conclusion that the principles employed in the TSVPP cannot yield 1s sample intervals. The use of improved hardware and software combined with geometry changes to the TSVPP tissue-interface can reduce the signal delay and the venous displacement magnitudes to enable fast sampling rates with unobscured data.

Several factors were observed in use that can affect the accuracy of the TSVPP device. These fell into three categories: the physical handling of the instrument, the anatomical structures of the observation site, and the determination of pressure equilibrium morphology.

The physical structure of the diaphragm is circular for simplicity of design, analysis, and handling. The displacements from the diaphragm aperture are naturally of greater magnitude in the centre than around the edges. This can be seen in Figure 4-20, which shows a cross section the diaphragm extending into free space. When coupled onto the tissue, there is also a pressure coupling region under the diaphragm with the best efficiency at the centre of the diaphragm and that diminishes as you approach the edges of the aperture. For this reason, there is an inherent loss of correlation between the TSVPP chamber pressure sensor value and the pressure communicated through the diaphragm, as the target vessel deviates from the central axis. With large diaphragm extensions, the pressure deviations are more significant. With short diaphragm extensions, the diaphragm is flaccid against the tissue, and the pressure deviations are very small. It is this principle that is explored in Figure 4-23. The data point at (-7mm) X-axis displacement exhibits substantial error in excess of the remaining data set. The remaining data points have noticeable error, but the values are +/- 16% of reference values for the positions near to the central axis. The 54% error value of the (-7mm) position is distinct relative to the remaining data.

Operator applied pressure of the TSVPP against the tissue was not observed as a significant factor in these studies, but there was only one operator, and no variability to help explore the sensitivity and boundaries of that parameter. Earlier bench work suggested that a practical working range existed that included normal handling without extreme effects on the accuracy of the results, and this was not contradicted in the observations of these animal studies.

Operator placement stability proved to be a factor in these results. The data from Figure 4-23 were collected from the same study over a short interval. Simply put, it was difficult to hold the
TSVPP steadily on the bony-ridge of a canine forelimb for a long period of time. This was in part due to the very narrow base afforded by the slender limb. It was also due in part to the movement of the diaphragm and to the elastic nature of tissue under that diaphragm. The instability of the device positioning is expected to be substantially mitigated by the fact that human limbs are generally larger and have a greater number of near-planar surfaces with accessible superficial veins. However it is certain that substantial optimizations of the physical form of the TSVPP can yield improved ergonomics and stability in use.

The final category of error causation is the identification of the pressure equilibrium event. The very definition of pressure equilibrium changed from that observed in the bench tests to that observed in animals. The transition from open to occluded vein structures appeared within 3-5 mmHg in most cases, and the pressure equilibrium definition of a flattened vein wall yielded to a new definition of a collapsed vein. This may be largely a consequence of the physiological veins responding differently than the bench level counterparts, and it may be partly due to operator bias that a closed vein is easier to identify than a flattened vein. When both occur within a few millimetres of mercury, the functional values of the results are not significantly compromised.

Identifying vein closure is not always clear and simple. There are several factors apparent in the data that complicate this task. Some veins are easier to identify than others. Some veins are adjacent to other veins or arteries that confuse the image a closure. In some placements, intraluminal valve leaflets can be seen in the image and these can confuse the eye. There are factors in the imaging domain too that can affect closure identification: Dynamic range, ultrasound frequency, contrast settings, ultrasound probe type and other imaging factors can impact the clarity and detail available to identify closure. Good ultrasound skills are a prerequisite for effective use of the TSVPP, but careful selection of the target site will significantly improve the prospects for accurate data recovery. A redesigned version of the device over that used in this study might employ automated methods for identifying venous equilibrium events and reconstruct pressure readings in real time.

4.4 Conclusion
The evaluation of the TSVPP across several animal models demonstrates the feasibility of the instrument for non-invasive pressure measurements with potential clinical utility. The accuracy of the Very Slow and Slow mode data were acceptable across a wide range of venous pressures. An $R^2$ fit values of 0.94 to 0.98 were achieved in Slow and Very Slow sampling modes for the ovine and canine models. The corresponding slope ranges were 0.92 to 1.09. The accuracy of fast mode sampling was very poor. The correlation was negative for the evaluation conducted. Thus the utility of Fast mode was not established. However the factors that confounded this mode of operation have been identified. These factors are implementation and evaluation specific. They do not, in principle, prevent TSVPP operation at fast sampling rates. The substantial utility of TSVPP approach in slow modes can be argued on the basis of the physiological data presented, and a range of design improvements and technique improvements have been identified for future development.
Chapter 5
Healthy Volunteer Studies
5.0 Introduction

Following from the initial bench testing (Chapter 3) and animal studies (Chapter 4) this chapter will focus on testing using human subjects. A major objective of the healthy volunteer study was to gain human-specific experience with the TSVPP and to establish the relationship between hydrostatic venous pressures and data from the TSVPP. The hydrostatic pressures were not measured directly, but were calculated from anatomical dimensions, vertical displacement measures, and physical principles [24, 127]. This approach to obtaining control data is not direct, as was the venous cannula manometer described in animal studies of Chapter 4. However the use of cannula measurements is highly invasive and carries the risk of vein damage and infection. The responsibility of engaging these risks in otherwise healthy subjects, the availability of alternatives, and the lack of prior human evaluations with a device of this nature, either in our experience or in the literature, supported an ethical choice to pursue non-invasive reference values for this healthy volunteer study.

The use of reference points, dimensional measurements, and physics principles allows the comparison of the TSVPP measured static venous pressure in the lower limb with the calculated haemostatic pressures that resulted from three defined postures. The results provide a data set that was used for optimization of the technique. The utility and practical considerations of the TSVPP are considered, and possible system enhancements are also described in this chapter.

5.1 Methods

5.1.1 Participants

The study protocol described and performed was approved by the National University of Ireland Galway Research Ethics Committee. The original research ethics application form, protocol documents, patient information sheet, supply checklist and data sheet are attached as appendices. Twelve healthy volunteers were recruited. In summary, exclusion criteria included history of vertigo or dizziness, venous hypertension, venous ulcers, deep vein thrombosis, or open wounds on the foot or lower leg. Inclusion criteria included adults 18 to 65 years of age. Participants had to be in good health and able to stand, sit, and lie for up to 10 minutes with the help of a stabilizing frame. They were required to be able to perform 10 heel-raises within 30 seconds. Participants were informed they
could withdraw from the study at any point without giving a reason. Prior to inclusion, volunteers were provided with an information sheet to review, and invited to ask questions. They were asked to read and sign the consent form after giving due consideration. Each subject was given a random 3 character identifier used on subsequent data files. Data were obtained for each patient in order to establish a basis for estimating the vertical offset between the mitral valve and the site of vein observation. These data included:

- Patient height (cm)
- Sternal length (cm)
- Sternal notch height (cm)
- Vein observation site to sternal notch vertical distance (cm)
- Gender
- Age
- Optional photographs of vein observation site

5.1.2 Protocol Setup

The subjects’ height, sternal notch heights, and sternum lengths were measured to estimate the position of their mitral valve [24, 128]. The level of the tricuspid valve was calculated to be 10% of the vertical distance from the xiphoid notch to the suprasternal notch. This was estimated from anatomical drawings, x-rays of implanted tricuspid valves, and a discussion with a practicing interventional cardiologist [124]. Rules for establishing the Phlebostatic Axis have varied considerably over time and by author [24, 123, 125]. This author’s estimate is not purported to be extremely accurate or precise. Its function is to provide a plausible and consistent estimate of zero pressure level.

Subjects were asked to assume one of three postures and remain still for 3-5 minutes in each position. The order of postures was selected by a random number generator. These postures include standing, sitting with legs perpendicular to the floor, and sitting with legs extended parallel to the floor (Figure 5-1, Figure 5-2, and Figure). In each posture, the vertical distance between the vein observation site (O) and the sternal notch (S) was measured.
In each static posture, a short video capture was obtained of the vein cross section using B-mode ultrasound as it responded to the surface pressure modulations of the TSVPP. After a minimum 45s stabilization interval, ultrasound images of the veins were captured using the TSVPP system.
Additionally, volunteers were asked to stand and do 10 heel lifts within a 30 second interval. Ultrasound image data were collected immediately upon the cessation of the heel lifts.

5.1.3 Measurements and test sequencing:
The foot and ankle areas were examined for the presence of suitable observation sites, ‘O’. The criteria included a readily accessible and superficial vein that was located on a substantially planar region of the foot. The dorsal aspect of the foot was preferred, but it was allowed that veins near the lateral malleolus and medial malleolus would also be suitable also Figure 5-4. The site had to be accessible for the TSVPP and comfortable for the volunteer. Upon interrogation with the ultrasound imager, the vein had to be well defined. A relatively straight section of vein that did not branch nearby the observation point was desired. Similarly, veins or arteries crossing under were avoided as much as possible.

![Observation landmarks for TSVPP evaluations on the lower limb](image)

Figure 5-4 Observation landmarks for TSVPP evaluations on the lower limb

The distances from the floor to the horizontal plane of each of the indicated sites was recorded while the volunteer was standing (H, S, X, and O). Once these preliminary data were obtained, the measurements relative to each posture were collected at onset of each subtest.

The order of testing was determined by the action of a random number generator implemented in an Excel spreadsheet. Once each posture was established, the vertical offsets for that posture were measured and the participant was asked to remain still for the duration of data collection. At least 45 seconds of stillness was required before the testing onset, to ensure that the limbs would fill with
blood and that the muscles of the lower limb would not be activated. This was to prevent the static pressure equilibrium from being modified through the action of muscular venous pumping. Testing at each posture included a collection of TSVPP data and typically required about 5 to 10 minutes. Most of this time was setup, guiding the subject, and finding a good initial image for the TSVPP. The actual venous pressure data collection typically required 2-3 minutes.

Following each collection of TSVPP data, the next posture was processed in the same manner until the final data set, which was not randomised, but was always the Ambulatory Venous Pressure (AVP) set. This was performed last to ensure the optimum collection of static venous pressures.

The AVP set consisted of asking the participant to stand with the help of a balance frame and then finding an accessible dorsal vein on the foot. The participant was asked to perform 10 heel rises within about 30 seconds in total. This action stimulated the calf venous blood pump. At the end of the 10\textsuperscript{th} heel-rise exercise, the TSVPP was set to a sampling mode, typically slow mode, and vein morphology and TSVPP pressure data were recorded for approximately 1 minute.

5.1.4 Data Analysis

Ultrasound capture frames were paired with instantaneous TSVPP chamber pressures as the veins transitioned from opened to closed states. The video data were processed for time-shift corrections between the TSVPP data and the B-mode video capture data as described in Chapter 4. The time-shift values were obtained by correlating the TSVPP pulse-width data with the pressure diaphragm displacements. The time shifts averaged about 250mS or about 8 frames of the 30F/S video record created by the laptop video-capture software. These corrected pressure data were mapped against calculated static pressures for each of the tested postures. An example of the healthy patient data is shown in Figure 5-5. No intravenous pressure data are available as in the animal studies, thus the absence of the time-pressure plot and the requirement to compare results to estimated pressures.

TSVPP observed pressures that deviated from the static estimated pressures by+/−35\% or more were reviewed to validate the data and/or to understand whether identifiable confounding factors produced measurement error. As the system is not real-time measurement capable in this prototype
implementation, the only actions possible for confounded data are exclusion and the modification of future test and instrumentation methods.

5.2 Results

The volunteer population consisted of 12 individuals, 9 males and 3 females. Ages ranged from 24 years to 47 years with a mean of 34.7 years. Their heights ranged from 163cm to 184cm with a mean of 175.9cm. The volunteer cohort parameters are tabulated in
Table 5-1 Volunteer cohort parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>175.9</td>
<td>163</td>
<td>184</td>
<td>6.2</td>
</tr>
<tr>
<td>Standing Jugular notch (cm)</td>
<td>143.8</td>
<td>133</td>
<td>152</td>
<td>6.1</td>
</tr>
<tr>
<td>Standing Xiphoid (cm)</td>
<td>124.5</td>
<td>116</td>
<td>132</td>
<td>5.3</td>
</tr>
<tr>
<td>Sternal length (cm)</td>
<td>19.3</td>
<td>17</td>
<td>22</td>
<td>1.5</td>
</tr>
<tr>
<td>Age</td>
<td>34.7</td>
<td>24</td>
<td>47</td>
<td>6.9</td>
</tr>
<tr>
<td>Total Subject Count</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5.2.1 Static Measurement Data

Table 5-2 describes in summary statistics the differences between the calculated values of hydrostatic pressure in the test subjects and the pressure values measured using the TSVPP. The data in this table are comprised of the 64 static pressure readings that were not subject to an overt error. Three ranges of expected pressure were obtained from the postures determined in the protocol. In the leftmost column of Table 5-2, the average expected pressure values are obtained from the mean of the calculated expected pressures for each posture.

The estimated pressure is calculated by: \( P_e = \rho gh \), where \( \rho \) is the density of blood, \( g \) the acceleration due to gravity, and \( h \) the height difference between the physiologic zero point and the point of observation. This estimate assumes that the subject’s venous system is in a steady state condition and that the veins are not actively refilling from recent postural changes or muscular contractions.

Two TSVPP sampling modes were performed on each volunteer in each posture, Very Slow and Slow. The average expected pressure column of Table 5-2 indicates the mean of the expected pressure calculated from the 12 subjects. This column indicates the pressure range of the data set on the corresponding rows. The Error Characteristics column labelled ‘Average’ is the mean of the individually
measured values minus the paired expected values as calculated from the anatomical landmark measurements. The %Avg and %RSD are the average error values and sample standard deviation of the discrete error values divided by the average expected value and expressed in percent. The %Avg error and %RSD diminish with increasing pressure range. Each test condition was measured 3 times per subject for most subjects. Of the 72 subject, posture, and TSVPP mode combinations, 63 were measured in triplicate, and the remaining 9 combinations were measured twice.

Table 5-2 Aggregate TSVPP measurement characteristics The left most column reports the mean of the expected pressure range. The error characteristics columns indicate the most negative, most positive, and average error values. These are followed by percent average error and percent sample standard deviations.

<table>
<thead>
<tr>
<th>Test Conditions (Average Expected (calculated) Pressure)</th>
<th>TSVPP mode</th>
<th>TSVPP Samples</th>
<th>Error Characteristics (mmHg) or (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: 20.1 mmHg</td>
<td>Slow</td>
<td>36</td>
<td>Min -3.1 max 10.8 Average 4.2 %Avg 21% %RSD 21%</td>
</tr>
<tr>
<td>V-Slow</td>
<td>31</td>
<td>0.7 max 14.2 Average 7.3 %Avg 36% %RSD 22%</td>
<td></td>
</tr>
<tr>
<td>Med: 59.5 mmHg</td>
<td>Slow</td>
<td>36</td>
<td>Min -16.8 max 8.2 Average -5.3 %Avg -9% %RSD 13%</td>
</tr>
<tr>
<td>V-Slow</td>
<td>34</td>
<td>-4.8 max 16.1 Average 4.5 %Avg 8% %RSD 11%</td>
<td></td>
</tr>
<tr>
<td>High: 94.8 mmHg</td>
<td>Slow</td>
<td>36</td>
<td>Min -25.1 max 3.9 Average -8.9 %Avg -9% %RSD 8%</td>
</tr>
<tr>
<td>V-Slow</td>
<td>34</td>
<td>-16.4 max 10.9 Average -1.2 %Avg -1% %RSD 9%</td>
<td></td>
</tr>
</tbody>
</table>

The pressures measured by the TSVPP system and the expected pressures for each of the three static postures are shown in Figure 5-6Figure 5-7Figure 5-8. Each of the outliers with an identifiable special cause has been highlighted and labelled.

9 %Avg = Average of (TSVPP-Expected)/Expected; %RSD = (Sample Standard Deviation (TSVPP-Expected))/Expected.
Estimated and Measured Pressures for Healthy Volunteer Study (Low Range)

Figure 5-6 TSVPP pressure compared to calculated pressure (mmHg) values, for 12 subjects; Low Range. Outliers are encircled and tagged with error reference, see discussion for details for each error.
Figure 5-7 TSVPP pressure compared to calculated pressure (mmHg) values for 12 subjects; Mid-Range. Outliers are encircled and tagged with error reference, see discussion for details for each error.
A direct comparison of results by sampling rate for each volunteer is shown in Figure 5-9. The R-squared value is 0.939 and the slope is 1.11. There is observable disagreement between the results of the two sampling rates.
5.2.2 Dynamic Measurement Data

Dynamic pressure measurements, conducted immediately subsequent to standing heel raises, were collected to evaluate the potential for obtaining time-sampled Ambulatory Venous Pressure (AVP). *Fast* mode trials were conducted on two volunteers, but stable *B*-mode video imaging was difficult to obtain reliably using the *fast* mode. Therefore, *slow* mode was used on the trials of the remaining ten volunteers. The AVP record for one trial was not convertible to pressure because the TSVPP orientation was longitudinal. One of two data records taken at the fast sampling rate is shown in Figure 5-10. Error dominates the signal, and the classic AVP response is not apparent. The dashed line in the figure represents the monotonically increasing pressure response expected in a stationary subject immediately following the heel raise exercise. The observed results have no
correlation to expected normal behaviour, and the values fluctuate rapidly between high and low values in a non-physiologic manner. The second fast data set exhibited similar behaviour.

![AVP Trial Using Fast Mode](image)

Figure 5-10 Fast mode AVP responses.; Error dominates this response. Dashed line represents the expected response characteristic.

Nine records taken at the slow sample rate were converted to pressure plots. Of those data, five slow AVP data sets produced recognizable approximations to a classic AVP curve. Four data sets were dominated by measurement error and did not demonstrate expected AVP characteristics. Figure 5-11 depicts the AVP results captured using the slow sampling rate mode. Sample measurement error is evidenced by the irregularity of the curves. However, the general monotonic increasing pressure characteristic is apparent.
5.3 Analysis and discussion

Of the 72 static measurements captured, 8 appeared to be flawed upon review, thus 64 static measurements were included in the results. Table 5-3 lists a number by type of the overt imaging flaws that confounded the conversion of some TSVPP observations into pressure measurements. Some TSVPP observations included in the results demonstrated these problem types to lesser degrees, but those were sufficiently clear to enable pressure measurements.

Table 5-3 Imaging problem incidents

<table>
<thead>
<tr>
<th>Problem type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation</td>
<td>4</td>
</tr>
<tr>
<td>Artery vein confusion</td>
<td>2</td>
</tr>
<tr>
<td>Poor vein wall definition</td>
<td>2</td>
</tr>
</tbody>
</table>

The general quality and resolution of the measurements was impaired by the slow frame rates afforded by the ultrasound system. 15F/s was the minimum frame update rate used in this study. The TSVPP readout-panel video acquisition captured at 30F/s. Some offset and timing mismatch occurred.
between the two frame rates. Therefore data were updated at a max of 15F/s, but there was commonly a 30F/s offset, between TSVPP pressure updates and video updates. Additionally, lost video frames in the capture card were frequent enough to present in the data several times. These typically appeared as a static B-mode frame that failed to update for 3 or 4 TSVPP frames. Table 5-4 provides an index with details of the anomalies associated with 8 out-of-range pressure values. These are labelled (a-h) in the Figure 5-6Figure 5-7, and Figure 5-8.

Table 5-4 Details of special cause anomalies observed in TSVPP static measurements.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>A small artery was mistaken for a vein. A small off-centre vein in the viewing field was used, but the image was terrible and virtually useless. Image quality and user error.</td>
</tr>
<tr>
<td>c &amp; d.</td>
<td>A large angle of incidence of the probe. Also, vein walls appear thick, as the vein doesn't collapse into compact bright lines as expected. User error, anatomical variation.</td>
</tr>
<tr>
<td>e.</td>
<td>Trench view here is difficult to read. Image quality and user error.</td>
</tr>
<tr>
<td>f.</td>
<td>This is a very difficult data set to read. The vein seems not to close fully, even though it is compressed and in motion with the tissue. Root cause of closure anomaly undetermined.</td>
</tr>
<tr>
<td>g &amp; h.</td>
<td>Sample vein is positioned superior and central to a large artery. The proximity appears to skew the response. Triple checked data, and no credible reading of the vein equilibrium event results in a pressure value anywhere near the expected value. User error and possible anatomical interference.</td>
</tr>
</tbody>
</table>

The results of this study included 64 successful static pressure estimations from 72 observations. Over the 64 valid results, the mid and high pressure average error was within +/- 10%. The worst reported individual error was 25.1%. It is noteworthy that these error metrics are obtained by comparison against an expected value, itself derived from anatomical landmarks and first-principles of hydrostatics. This study did not enjoy the advantage of a calibrated reference pressure to eliminate many sources of error left unaddressed by the landmark pressure reference technique. Thus the error estimates of these studies comprise both TSVPP errors and estimation method related errors. Of the 8 attempted measurements that were either clearly erroneous, or non-recoverable from the data records, 6 instances were due to operator error. The two remaining failed measurements were associated with arterial adjacency to the site under evaluation. Had the instrument provided real-time data, these measurements would have been retaken, but the current prototype only provides results following post-processing. The overall rate of operator error is likely to diminish with experience, but there will
always be challenges associated with finding a good evaluation site in some subjects. The actual
success rate for obtaining static venous pressure data in this study was 88%, and given that regular
users of the device would make fewer errors, the system may be capable of 97% success rate in this
mode.

The variety of the anatomy explored in this study far exceeded the variation found in either
bench or animal studies. The variety of surface angles, supporting tissue topology, operator position
variability, and the interaction with conscious subjects markedly increased the challenge of
positioning the TSVPP properly and controlling the test conditions for data collection. Imaging flaws
confounded more data than anticipated, and these were in part due to the aforementioned challenges.
While there were 7 data points that were excluded with image quality as full or partial cause, it is
certain that other data, though not excluded, were affected. It was apparent during the detailed data-
review, that the resolution and repeatability of included data were diminished by the lack of acuity in
the differentiation of venous structures from surrounding tissue. It is expected that refinements to the
TSVPP probe and optimizations to the ultrasound interface with that probe will yield improved image
quality in future devices.

The recruitment of volunteers was successful. The average age was 34.7, the youngest 24, and
the oldest 47. While this is far from a geriatric population, the cross section is old enough to have a
greater possibility of venous function compromise than the group of traditionally aged college
students. This may have some bearing on the AVP section of the tests, where venous valve
incompetence may be observed as shortened pressure recovery intervals. It is reasonable to consider
that the AVP profiles, had they been collected using traditional methods, would have demonstrated
variance in the recovery times. Given the lack of control data for the AVP results, the only true
guidance for estimating the credibility of the response curves is the expectation of monotonically
increasing pressures, starting from the cessation of exercise and terminating near or about the
maximum expected static pressure [42, 56, 129, 130]. These characteristics are found in the five plots
of Figure 5-11.

Slow video frame-rates proved significant contributors to inaccuracy at higher chamber sampling
rates (fast mode). This is due to larger pressure changes that occur between successive video frames.
Additionally, the rate at which chamber pressure changes is non-linear in use, and can increase due to the tissue resistance changes near the moment of equilibrium.

When the diaphragm is unrestricted, the change in chamber pressure is relatively linear through the pump displacement range. In clinical use, the diaphragm resistance is augmented by the tissue displacement resistance. This is negligible through a portion of the stroke, but then increases rapidly just at the point where the vein is fully collapsed and the only the tissue and diaphragm tension resist displacement. Thus \( \frac{dP}{dt} \) increases markedly near the interval of vein closure, and the effective data rate, in terms of mmHg / frame, decreases near the instant when it is most advantageous for it to be rapid. This causes under-sampling of the vein closure event. The result is increased error in the pressure data. At Very Slow pressure sampling rates, this is not a problem. At the more useful Slow rate, some error due to frame rate under-sampling is apparent in the AVP data. At the Fast sampling rate, the AVP data is too noisy to be usable, resulting in data characterized by the chaotic plot of Figure 5-10.

Frame-rate mismatch and lost frames impacted all the data in this study. While the worst of the data points had imaging or user-mediated deficiencies that overtly increased error magnitudes, much of the data have error magnitudes greater than expected for a clinical device, and well outside the potential accuracy of the TSVPP approach. This impact is reflected in the standard deviation of the static pressure results and in the noise that is apparent in the AVP plots. The best of the AVP plots demonstrate noticeable precision errors. The worst of the AVP plots are useless. While not the only source of error, frame rate mismatch and lost frames are substantial contributors.

The absence of real-time results that feed back to the operator has had a significant impact on the quality of these data. In particular, the 8 ‘lost’ static measurements would very likely have been repeated had the user been able to see the immediate results. On reviewing the data, there are clear instances when a deficit in sonographer skills, either of interpretation or operation, contributed to poor data. In a clinical use environment, the user would generally be trained to a higher level of skill and be well prepared to minimize some of the operator errors. However, all operators make errors and corrections. Real-time data feedback would enable corrections to be executed immediately.
Despite many shortcomings of design and execution, it is important to note the TSVPP system and operator collected 64/72 static data sets that are recognizable as analogous to predicted pressure values. This is a novel contribution to the state of the art.

While one aim of this study was to learn about the capability and deficiencies of the TSVPP approach, not all the apparent pressure deviations seen in the plots are errors. Because of the venous muscle pump action, and because these were conscious adults in an artificial situation, there are real pressure variations underlying these data. A subtle shift of body weight, muscle tension, and nervous motion on the part of subjects all contribute to fluctuations in the lower limb venous pressure.

The difference in the Slow and V-Slow mode data appears significant. There is a trend in the data for the Very Slow measurements to be generally higher values than the Slow measurements taken on the same patients in same postures. Figure 5-9 summarizes this effect in the slope value: 1.1147. Acknowledging that not all 5 digits are significant, a reasonable interpretation is that pressure tends to be reported 10% higher with the Very-Slow pressure sampling mod than with the Slow mode. The assumed conditions of the test are that there is a steady-state venous pressure under observation and that the measuring system does not affect the measured parameter. Given this premise, the expected outcome from sampling the same event with different precisions would be an increase in reported variance without a change in the mean values. However the opposite has occurred. The variance is relatively constant across methods, but the mean values have increased. This indicates that one or more assumptions are incorrect.

A review of the methods employed in the study finds that the order of postures was randomized, however the order of measurements within postures was not randomized. Slow measurements were taken before V-Slow measurements in all patients. One explanation therefore, is that the pressures had not fully equilibrated in all patients when the first data were taken. Additional vein filling occurring during the Slow Rate testing phase, would present a dynamic pressure signal to the TSVPP that would increase over successive measurements and result in greater pressure variance. An additional consequence would be actual venous pressures would tend to be higher in the later phase of data collection when the V-Slow measurements were obtained. The study design called for a waiting period to stabilize limb pressure in each posture prior to measurement, but there was no calibrated
reference pressure to establish that the limbs had achieved that stability. There was no system to indicate that the pressure equilibrium was disturbed in any way. Thus the difference Slow and Very Slow measurements may be reflecting real changes that were not isolated by the study design and execution.

A final note about the conversion of B-mode video to vein closure events is warranted. These data were extracted by observing frame-by-frame data and estimating when pressure equilibrium had occurred. This subjective identification of vein closure was difficult to regulate and make routine. Ultimately, the definition of venous closure as a human decision introduces subjectivity to what is ideally an objective measurement process. The value of repeated pressure measurements with multiple operators might vary significantly, as each operator interprets the b-mode image and the vein closure differently.

Image sets from the equilibrium phases of the animal studies were used as the guidance for these evaluations. However, each vein in each posture has a unique profile. Changes in the ultrasound beam angle, variations in the underlying substrate, and slight positional variations changed the view of the veins. A better indication of vein closure would be any method that has greater repeatability than human visual interpretation, even if this included a positive or negative bias to the automated indicator. A consistent bias could be compensated in an algorithm. While a number of automatic methods are conceivable. It is an open question whether machine reading will be immediately better than human reading in establishing the equilibrium moment. That task is complex. However, it is definitely desirable to simplify and regulate the identification of the equilibrium moment, as this defines the measurement value.

5.4 Conclusion

In a significant and novel contribution, TSVPP device produced serviceable data for static measurements that have the potential to be highly accurate with basic improvements to hardware. The TSVPP shows promise for the purpose of obtaining AVP data, but will require hardware and software changes to improve the temporal resolution and pressure accuracy at high pressure-sampling rates.
Successful use of the TSVPP requires good operator technique and training. Especially in human clinical use, there is much variation in anatomy and operating conditions that must be accommodated.

Importantly, the principle of the TSVPP appears sound. Despite noise in the data, the results indicate the method can sample steady-state and dynamic pressure events. The dominant error sources in these data have been identified, and technical means to mitigate them are practically achievable. Among them, automatic vein closure identification seems essential to collect reliable AVP measurements. The post-measurement manual review used in this study is impractical for clinical work. However, it would be possible to use manual equilibrium identification for static pressure measurements.

As a practical device, the TSVPP should be closely integrated with the ultrasound imager. Direct access to the image stream with concurrent signal processing of pressure values and the video would eliminate many of the flaws identified in this study. The TSVPP might also benefit from a remote pump design, and the probe housing may be much easier to handle in that configuration. The pressure chamber and sensor would remain on the probe. The standoff from the fluid chamber provides a clarity benefit for superficial structure imaging, and the sensor can be so small as to be fully unobtrusive.

Many design improvements relate to the software and algorithms of the system. The need for a faster video sample rate, the possibility of closed-loop pressure-sampling, auto closure identification, and artery identification can be realized in software and firmware. As a demonstration of the potential for the TSVPP device, this study highlighted many factors that impact the overall functionality. Many design improvements, and several handling improvements were identified in this study. Despite the many limitations and improvements identified here, the prototype TSVPP has demonstrated a novel and significant improvement to the non-invasive evaluation of peripheral venous pressures that can provide useful physiologic data with clinical utility.
Chapter 6
Conclusions and Discussion
6.0 Conclusion

The work described in this thesis resulted from a desire to obtain intravenous pressure information without the requirement to perform an invasive venepuncture. This followed from a programme of research by the Bioelectronic Research Cluster at NUI Galway into circulatory disorders of the lower limb, and in particular focussed on the clinical application of Neuromuscular Electrical Stimulation techniques to enhance venous circulation and to mitigate circulatory diseases. From this background of research, arose an interest in the available evaluation modalities for assessing a variety of parameters associated with the venous system, in particular, the venous pressure in the lower leg.

A review of the venous physiology of the lower limb has supported an understanding of the normal functional behaviour and interactions of the vessels, venous pressure, and muscle pumps. The generation of static venous pressure from the hydrostatic column imposes a continuous stress on the venous system of the lower legs in particular. The static pressure is referenced from the zero point of the right atrium, and increases with vertical drop. The basis of the need for this work is that without the compensatory functions of the venous valves and muscle pumps, there would be inadequate return of venous blood to the heart, and the venous pressure of the foot would be excessive and unremitting [26, 42, 105, 131]. Compensation techniques such as IPG and NMES of the calf muscle pump would be expected to result in a reduction in venous pressure, and the development of a non-invasive means of venous pressure observation is desired.

We have seen that the failure of the venous muscle pump can be a primary cause of chronic venous insufficiency or a secondary consequence. The severity of chronic venous insufficiency is graded according to symptoms on the CEAP scale. At the most severe end of the scale, chronic venous ulcers are persistent. These ulcers are debilitating, painful, socially limiting, and difficult to treat. The economic and social costs of chronic venous ulcers are significant, and the need for improved therapies and diagnostic tools is substantial [45, 46].

Since venous hypertension has been established as a cause of venous ulcers and is indicative of chronic venous insufficiency, common therapies attempt to mitigate either the pressure or the effects
of abnormal venous pressures. The NMES therapies in development at the Bioelectronic Research Cluster stimulate venous flow from the lower limb by actuating the muscle pump with the expectation of a concomitant reduction in venous pressure. Our laboratory observations of direct circulatory effects are non-invasive, and primarily have been the velocity and flow parameters obtained with duplex ultrasound. Yet a review of pressure measurement techniques has revealed that the gold-standard pressure measurement for chronic venous insufficiency is the invasive technique of Ambulatory Venous Pressure. This provides static and dynamic venous system parameters not available from non-invasive methods [10, 13, 40].

The progression of pressure measurement instruments has been dominated by invasive devices, which while increasingly precise, pose the risk of infection or vein damage. Non-invasive pressure measurement has been well-developed for the arterial side of the systemic circulation, but these techniques are ill suited for peripheral veins. The advent, and near ubiquity, of ultrasound instruments has inspired some researchers to consider the application of these devices to the problems of central venous pressure measurements. These are often taken from central lines in the superior vena cava, and share risks similar to invasive AVP measurements, such as of infection, dislodgement and vessel damage [71, 85].

The work of Baumann was the first to estimate central venous pressure by ultrasound image-guided compression of the jugular vein. Aggarwal developed a similar approach with a system to easily store the force required to close the jugular vein whilst observing the vein morphology on an ultrasound imager. These techniques were non-invasive, and used ultrasound as a detection method, but they were not sufficient for the stated application requirements. They were limited to static pressure measurements, used only manual control, lacked the capacity to continuously record the applied system pressure, and did not have cyclic pressure-sampling features. However, they clearly suggested that more could be done with applied pressure and ultrasound to observe internal venous pressure. The synthesis of prior ultrasound pressure measurement attempts with the unmet requirement for AVP-like data became the basis for the TSVPP concept. The recognition that pressure data were desirable to augment the structural, velocity, and flow observations available using the
Doppler ultrasound method, has led to the proposal for a novel system that integrates these modes with time-sampled pressure detection.

The proposed system provides automatic or manual control of applied venous-collapse pressure in combination with cyclic pressure control to achieve a time-sampled reconstruction of the Ambulatory Venous Pressure curve. Realizing this functionality in a demonstration device presents substantial hurdles. The problem is inherently multidisciplinary; encompassing the integration of ultrasonic hardware, electronic controls, hydraulic pumps, mechanical design, physiologic and anatomical knowledge, pre-clinical and clinical evaluations, image processing, algorithm design, and software programming.

Despite the breadth of the technical challenge, or perhaps to a small degree because of it, the TSVPP appeared to be a worthwhile endeavour. The literature search and background studies indicated that this was an unmet clinical need with a broad field of application in clinical practice. Thus the work seemed justified by the possibility that it should offer benefits to the wider research and clinical communities.

The primary objectives of this work were elaborated early in Chapter 3. Briefly these can be described as the creation of a non-invasive pressure measuring system with the capability to observe static and dynamic pressure values in conjunction with a typical clinical ultrasound scanner. In particular, the recreation of an ambulatory venous pressure measurement analogue was envisioned. Since the pressure observations are acquired using a Doppler ultrasound system, the observation of flow, velocity and pressure characteristics are envisioned using the same instrument. The TSVPP objectives were refined by analysing the physiologic characteristics of the venous system, the frequency and magnitude characteristics of ambulatory venous pressure waveforms, and the general requirements for patient safety, comfort, and operational ease. Table 6-1 summarizes the parametric objectives of the instrument design and briefly summarizes the related results from the pre-clinical and clinical studies.
The TSVPP system was conceptualized in several ways before settling upon an approach with the desired balance of challenges. The initial concepts included the direct readout and recording of chamber pressure into the B-mode video record. Because of the limitations of the direct readout pressure resolution, the existence of highly accurate commercial pressure sensors, and the need to focus on the myriad system design problems that had no commercial solutions, the direct recording approaches were shelved. The design course finally selected used precision sensing and custom instrumentation coupled to a recording computer that integrated B-mode images, reference pressure data, and chamber pressure data.

The sensor scheme that allowed this system architecture employed a Honeywell bridge sensor typically used for gas pressure measurement. This was tested and calibrated with the mineral oil.
media used in the pressure chambers and the resulting calibration data sets demonstrated excellent accuracy and repeatability.

The mechanical assembly was designed to conform to the GE logiq-e ultrasound transducer housing whilst providing the structure for a custom displacement pump and diaphragm assembly. The housing and pump parts were modelled in solid works and printed using SLA technology. This allowed a progression of designs that moved from narrow chambers and slot apertures to wide chambers and circular apertures. A zero-tension diaphragm was developed to improve the low pressure accuracy of the system and the pump mechanism progressed from a moving-vane to a displacement piston type with improved capacity and reliability. The final mechanism survived over 15 months of testing without a failure.

An ultrasound machine video interface was created using a capture card and software that were combined with the custom software application for the chamber control and readout. These ran concurrently with firmware operating on the microcontroller that created the servo commands and converted the analogue pressure signals into digital data. The firmware was designed to allow the selection of several data collection modes and manage the bi-directional USB communications with a host computer.

The custom electronics required for this design were implemented using commercial instrumentation amplifiers, precision supplies, and an 8051 based controller. These were fabricated on a small printed circuit board and located in an aluminium housing with the command switches. The safety of the electronics was provided by double insulation, the use of medical grade power supplies, and the use of a battery powered host computer.

The system required substantial integration and testing prior to animal or human use, and bench vein models were created to provide a test platform and to generate reference data. These models were used to evaluate the impact of the tissue underlying the superficial veins and to assess impact of different vessel diameters. An approximate analogue for muscular and bony tissue was selected and comparative data suggested little difference in venous response between the two substrates. The bench model also provided a means to evaluate cross-section and longitudinal vein visualization modes. The cross sectional approach was found superior and was the chosen method employed for
further animal and human studies. The effect of operator holding force was evaluated and found to have no apparent impact on pressure readings.

The bench testing produced several iterative design improvements in the pump, chamber, housing, and diaphragm designs over three major prototype revisions. The software and firmware evolved and improved, and the use experience gave useful insight into the techniques that were later practiced in-vivo.

The completion of bench testing and the establishment of a stable mechanical, electrical and software design provided the impetus to conduct in-vivo testing on animal models. Testing was performed at the facilities of Boston Scientific and was conducted under their internal IACUC oversight. To qualify for the study, a literature search and rationale for the unique value of the data were required. Only after thorough review was permission granted. The studies employed animal models that were viable after un-related primary studies had been completed. Animals remained fully sedated from the onset of the primary study through duration of the TSVPP study without interruption. All animals were treated humanely, and the supervision of veterinary doctors was continuously present to ensure that appropriate procedures were applied.

The test protocol was designed to allow for the collection of simultaneous venous cannula pressure in the limb adjacent to the site of TSVPP operation. This provided unique and useful correlation data that were presented in the results section of Chapter 4. The correlation of cannula and TSVPP pressure measurements was good. $R^2$ values exceed 0.9 for the very slow and slow mode results. The fast mode data produced poor correlations that were determined to be the consequence of frame rate limitations.

These in-vivo data produced useful refinements to the identification of equilibrium states and resulted in the identification of sampling rate and position mediated measurement errors. In particular, the definition of pressure equilibrium as indicated by the flattening of the vein wall nearest the pressure diaphragm gave way to the definition as venous lumen closure. This was a significant change that was driven by the intraluminal pressure data of the animal studies. The range of pressures that bounded open and closed lumens were mapped in the video records, and near the equilibrium point, pressure deltas of just 3-5mmHg were seen to drive the vein from the inflated state to the
collapsed state. While this range of pressures is not an all or none transition across an infinitesimal pressure change, it is small compared to the working pressures of interest, and offers the possibility of practical resolution in a measurement system of this type.

The pressure control approach selected for the in-vivo study demonstrated that a range of arbitrary venous pressures could be regulated and observed in the limbs. It also produced some pressure artefacts with communicated arterial pressures and amplified TSVPP mediated pressure pulses. Overall, the in-vivo data provided device handling experience, correlation results, and system behaviour data that were invaluable and informed the use and interpretation of the TSVPP device in healthy volunteer studies.

Healthy volunteer studies were initially intended to include reference pressure data from an invasive catheter. However, the difficulties of obtaining ethical approval were substantial. An alternate plan was created that used volunteers without the cannulation procedure. The reference pressure was instead calculated using first principles of physics and anatomical measurements. Despite the absence of invasive reference data, the study generated substantial and useful results. The values of the calculated pressures and the measured pressures exhibited good agreement. The values of very slow and slow mode static measures demonstrated good agreement with a 11% positive bias to the very slow mode data.

The correlation of measured pressures to the calculated values was useful, but the identification of erroneous readings within the data set was also very interesting. Of 72 static pressure readings, 64 produced values that were in good agreement with the estimate values. The remaining 8 observations, when analysed, revealed that operator error was the primary cause for pressure estimation error. The modes of those errors were detailed, and the answers will inform future tests.

The ambulatory venous pressure testing segment of the human studies demonstrated that slow-mode sampling could render reasonable approximations in about half of the subjects. This testing demonstrated both the potential of the concept and the limitations of the prototype implementation. The handling of the assembly in fast mode, while maintaining steady contact with the limb, was difficult. This will be addressed in future designs as will the need for improved video sample rates.
These observations can be addressed with further design optimization and support the assertion that the principle can be implemented successfully.

The results of this work suggest that the novel concept of the TSVPP has the potential to be a useful instrument with research and clinical applications. Animal studies have shown good accuracy can be achieved for a first prototype system. Human studies have provided good agreement with theoretical values, and they have demonstrated an acceptable rate of successful pressure observations. The objective of a time sampled ambulatory venous pressure measurement tool was partially realized in some volunteers, and the approaches to realize significantly improved performance were identified.

The potential exists for this device to be improved and extended as a tool for evaluation in our pneumatic and NMES venous system therapy studies. If brought to a higher level of sophistication, it could be used clinically, in the evaluation of patients as an augment to conventional duplex ultrasound. This thesis has focussed on the applications and haemodynamics of the lower limb; however, the TSVPP may have extensibility into other areas such as the evaluation of venous fistulae for dialysis patients.

**Future work**

The TSVPP embodies novelty in several domains. The hardware configuration of an integrated programmable pump for an ultrasonic transparent pressure probe, the automated control of externally applied pressure for the estimation of dynamic internal pressures using ultrasound, the adaptive control of applied deflection pressures, and the derivative-limited control of applied pressures for optimal time sampling are a few of the novel concepts that are being prepared for patent submission.

Of these future-work concepts, the automatic detection of venous closure or automatic venous morphology estimation and closed loop operation of the pump using the morphology estimation data are the most important. Figure 6-1 illustrates a contrast method for detecting vein walls and estimating their separation. Other techniques can be applied and are described in the appendices, but the primary goal of all the morphology estimating techniques is automating and regulating the detection of closure. This will deliver two valuable results simultaneously: the systemization of closure events and the potential of feedback modulated vein closure rates by pump modulation. The systemization of closure identification may introduce systemic errors, but will eliminate human error. The systemic
error should be more predictable and more readily compensated in software, once properly characterized.

![Cross sectional shortening on the axis of applied pressure.](image1)

**Figure 6-1** One version of automatic vein morphology estimation.

The automatic detection of closure implies an ability to estimate in real time, the interval just prior to closure and the interval post closure. These information can be employed in several ways to improve accuracy and produce more frequent pressure measurements. Slowing the pump velocity just prior to venous closure allows more video frames to be captured around the event improving temporal resolution and pressure resolution.

Once vein closure has been verified in real-time, the displacement pump no longer needs to achieve maximum displacement. It can immediately return to a starting position and shorten the interval between pressure measurements. Figure 6-2 illustrates system behaviour achievable with automatic morphology detection in concert with closed loop control. Reduced pump velocity near pressure equilibrium, pump cycle shortening, and pressure loss estimations are used to provide optimum sample rates and accuracy for AVP type measurements. The system is conceived as a software/firmware implementation that can use the existing hardware system for development. However, practical real time control of this nature will require high speed image processing of the real time B-mode signals with minimum delay, implying an implementation closely coupled to the ultrasound instrument.
Figure 6-2 vein morphology observer mediated feedback control

Successive prototype systems can now be conceived that leverage the knowledge gained in this course of study, and it is hoped that improved clinical evaluations will demonstrate a heightened degree of system capability that will meet the needs of researchers and clinicians for high quality non-invasive venous pressure measurements that provide the benefits of invasive data without the hazards.

This thesis has explored a novel concept in venous pressure measurement and has extended the knowledge of its potential and its limitations with qualitative and quantitative evidence. The results support an assertion that the TSVPP has promise for improving our insights into clinical diseases of the venous system. Further, the TSVPP can be developed as a useful tool for evaluating the effects of venous therapies designed to reduce venous stasis and hypertension. A foundation of conceptual work, bench evaluation, pre-clinical tests, and clinical study has been established. Future development of the concepts and implementations discussed appear justified from the potential intellectual, clinical, and societal benefits that can be associated with the product of this work.
Appendices
APPARATUS FOR TIME-
SAMPLED DETECTION OF
VASCULAR PRESSURE

Confidential

Summary

- The system described here is a method to obtain direct readings of venous pressure in the lower limb using a small appliance in conjunction with a standard vascular ultrasound imager.

- The effect will be to provide both static and time-sampled measurements similar in utility to AVP data but without a venipuncture.

- The utility should be clinical quality information with reduced trauma and infection risk.
**Principle**

- Superficial veins are imaged using an ultrasound transducer whilst being compressed by a liquid-filled membrane.
- Membrane pressure is varied in a controlled manner.
- When the membrane pressure equals or exceeds internal venous pressure, the collapse can be identified on the monitor.
- The instantaneous pressure on the membrane is measured precisely and paired with the image of the vein as it collapses.

**Vessel Response to Chamber/Diaphragm Pressure**

(a) Chamber pressure less than vein
(b) Chamber pressure greater than vein

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Implementation

System Diagram
The slew rate of the fluid vessel pressure (blue trace) sets the maximum sample frequency of the system. A triangle wave assumes symmetrical positive and negative pressure slew rates. The positive pressure slew rate affects accuracy. Faster slew rate results in greater pressure delta between image samples and greater venous reaction pressures against the resistance of the vessel.

A sawtooth wave uses asymmetrical positive and negative pressure slew rates. The positive pressure slew rate can remain slow for the same slew rate accuracy result as the triangle wave. Faster negative slew rate results in shorter cycles and more rapid sampling of pressure data.
A closed loop feedback system between vessel closure detection and the pump servo will allow a constant pressure slew to allow faster maximum sample frequency of the veins. This graph is plotted using a “25 Over, 50 Under” rule. The positive pressure increases until 25mm Hg beyond the vein closure event. The negative pressure decreases until 50mm Hg below the vein closure event or to zero. This algorithm can be combined with sawtooth pressure waveforms for more rapid rates, but alone enables fast sampling with a simple servo drive system.

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This graph is plotted using a “10 Over, 25 Under” rule. The positive pressure increases until 10mm Hg beyond the vein closure event. The negative pressure decreases until 25mm Hg below the vein closure event or to zero. While the slew rate of the pump pressure is identical to all the other plots in this series, the number of samples is 25 compared to 8 for the initial concept.

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Comparison of reconstruction data with Triangle, Sawtooth, 25/50 and 10/25 Closed-Loop Triangle pump-servo drive schemes.

Vein Morphology Detection 1

Cross sectional shortening on the axis of applied pressure.

Contrast detection of the vein walls on an axis (yellow line above)
Vein Morphology Detection 2

Eccentricity: Ratio of axis lengths, or area by estimation of fitted ellipse

Vein Morphology Detection 3

Wall Curvature inversion
- Sampling lines are created parallel to the long axis and perpendicular to the applied pressure.
- The walls are inverted where the number of crossing points changes from 2 to 4.
- This technique can be used in combination with dimensional analyses.
Vein Closure Estimation 1

- Evaluate a vein morphology parameter e.g. Minor axis diameter, as shown to the right.
- Plot that parameter as a function of pressure.
- Fit the parameter to an asymptotic curve e.g. exponential decay or a sigmoid function.
- Predict the closure based on the trajectory of morphology distortion through a percentage of the possible range. e.g. from 10-90% of possible closure for a distance, or for 90-10 percent aperture for area type measurements.
- One advantage is accommodating the non-linear responses of the vein to pressure changes near the fully closed condition.

Vein Closure Estimation 2

- Evaluate a vein morphology parameter e.g. Minor-axis length, ellipse-fit area estimate, Minor/Major axis ratio, etc.
- Map that parameter as a function of pressure.
- Fit the parameter to an asymptotic curve e.g. exponential decay or a sigmoid function (in this case \(1/(1+e^{-x})\)).
- Predict the closure based on the characteristic of the fitted curve.
- Select a the closure identification criterion based on the derivative(s) of the fitted curve.
- 1st, 2nd, 3rd and even higher derivatives either singly or in combination can be used to select the desired transition on the curve.
- One advantage is apprehending and predicting the venous morphology changes. These occur rapidly near to the closing pressure.
Closed Loop Servo Control

This algorithm implements the change of chamber pressure direction upon the detection of a vein morphology transition.

- A vein morphology observer feedback loop to the servo controller allows the possibility of dual rate pressure ramps. Rapid ramping occurs until the initial indication of venous changes are detected. Then a slower ramp is driven until vein closure is declared.
- The slower dwell rate results in better pressure resolution due to decreased pressure delta between vein closure detection samples. Note that the 10/25 algorithm was also employed. The rapid pressure drop early in the AVP waveform exceeded the parameters of the 10/25 algorithm, and some data points were missed as the pump ran an extra full cycle without detecting the vein pressure.
- The selection of the over/under hysteresis values must be made with consideration to the hemodynamics of the observed system.
- A "Sample Missing" detection and alarm algorithm would detect pressure transition cycles that lack vein closure detection events and alert the operator.
- An excursion limit threshold for the slow ramp can reset the pressure chamber after a selectable pressure rise, reducing the interval until closure detection occurs exist.
Integrated Pressure Indicator

- The pressure chamber can be fitted with a direct pressure indicating structure consisting of struts of various lengths configured to collapse at calibrated pressures. The collapsed will change the acoustic reflection of the members which will be detectable on an ultrasound monitor.

The internal volume must be fluid filled with an atmospheric pressure vent.

When a strut is deflected from a pressure differential, the ultrasound reflection changes as the indicating strip contacts the strut.

The device can be implemented in a standalone probe shield. This photo is of a commercial vascular ultrasound standoff of the type used to enhance superficial resolution.

The pressure indicator can be integrated with the face of the standoff.

Similarly, the indicator can be integrated with the pressure chamber assembly.

Method of fabricating a pressure-transfer diaphragm with a ‘zero’ tension displacement window.

- As a flexible pressure chamber membrane changes shape in response to transmembrane gradient, reaction forces are created. These forces are a source of error.
- The blue trace represents a pressure/deflection curve for a sheet of silicone rubber acting as a diaphragm.
- The red trace represents a more desirable curve with a distinct ‘zero reaction’ deflection range.
- A membrane can be created with an arbitrary ‘zero reaction’ deflection range by locating the membrane in an aperture, deflecting the membrane to the desired deflection, and then bonding the membrane at the aperture edges.
- With silicone rubber membranes, the hyper-elasticity of the silicone allows for large deflection ranges. RTV adhesive effectively bonds the membranes to the aperture.
- The result is durable and predictable.
Closed Loop dP/dt Control for improved pressure measurement precision

Hydraulic dP/dt Limiting for improved pressure measurement precision
Chamber Pressure Cycle Control for Optimal Sample Rate
Effect of dP/dt Limiting on pressure as the diaphragm transitions from free expansion to restricted expansion

Note the slightly decreased slope of the dashed trace in the free expansion zone. In the restricted expansion zone the dP/dt (approximated as slope in the figure) can be attenuated markedly (0.2x) in the dP/dt limited example. This effect can be realized with several physical structures, at the cost of increased piston displacement volume to accommodate the dP/dt buffering displacement volume.
Appendix B: Related Patents

**United States Patent**

**Janssen**

- Patent Number: 4,566,462
- Date of Patent: Jan. 28, 1986

**Abstract**

Venous pressure is measured by monitoring blood flow in a vein with a Doppler probe, exerting pressure on the vein downstream of the probe with a cuff inflated at the rate of 10 mm Hg/second or more and recording the pressure at the instant blood flow stops. The cuff is immediately deflated. Measuring apparatus is also disclosed.

**Claims**

8 Claims, 2 Drawing Figures

**References Cited**

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(54) PRESSURE Tourniquet WITH ULTRASOUND WINDOW AND METHOD OF USE

(75) Inventors: Arthur W. Zikorus, San Jose; John D'Angelo, Morgan Hill; Brian F. Farley, Los Altos, all of CA (US)

(73) Assignee: VNUS Medical Technologies, Inc., San Jose, CA (US)

( *) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(c), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 09/322,326
(22) Filed: May 28, 1999

Related U.S. Application Data


(51) Int. Cl.7 .............................................. A61B 8/00
(52) U.S. Cl. .............................................. 600/437; 600/443; 600/203
(56) Field of Search ................................. 600/485; 480; 483; 489; 490; 495; 588; 453; 455; 600/202-203

(56) References Cited

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(74) Attorney, Agent, or Firm—Fulwider Patton Lee & Uscell, LLP

(57) ABSTRACT
A pressure tourniquet having a window transparent to ultrasound is wrapped around a leg or another anatomical structure containing veins. An ultrasound transducer is placed in contact with the window of the tourniquet. The window is adjacent the anatomical structure and the transducer probes a dilated vein with ultrasound. The transducer can measure the size of the vein and detect reflux. A pneumatic bladder on the tourniquet is inflated to apply pressure to the anatomical structure so that the vein is compressed by the tissue of the surrounding anatomical structure. As pressure from the tourniquet reduces the diameter of the vein, competency of the vein valve can be temporarily restored to indicate the proper reduced diameter required to restore venous function. An electrode catheter is introduced into the vein to apply energy for durably molding the vein to the reduced diameter.

37 Claims, 6 Drawing Sheets
Apparatus and methods for non-invasive measurement of a subject's venous pressure, and particularly the subject's central venous pressure (CVP). The apparatus comprises a probe with a load cell. The method makes use of a non-invasive medical device or technique, such as an ultrasound system, to visualize the internal jugular (IJ) vein. Once the IJ has been located, the operator pushes on the surface of the neck with the probe until the external pressure is sufficient to collapse the IJ. The load cell within the probe determines the amount of force applied, and the applied force is converted into venous pressure.
An instrument for at least estimating physiologic pressure such as central venous pressure (CVP) non-invasively includes an ultrasound probe coupled to a display that shows the deformation of a vein as pressure is applied outside the body through the skin and soft tissues. A pressure transducer is applied to the skin to compress a vein, and an indicator coupled to the transducer shows the amount of pressure being applied when the ultrasound probe shows that the vein has collapsed. In the preferred embodiment, the transducer is an inflatable balloon filled with a liquid such as water, and the indicator is in fluid communication with the balloon. The indicator may be a mechanical gauge or meter, or may include a material that converts applied pressure to an electrical signal, in which case the electrical signal may be interface to a numerical readout. At least the probe and the transducer are preferably disposed in a hand-held housing.
ULTRASONIC MONITORING DEVICE FOR MEASURING PHYSIOLOGICAL PARAMETERS OF A MAMMAL

Inventors: Ronald S. Lisiecki, Libertyville, IL (US); Tamas Ban, Round Lake Beach, IL (US)

Assignee: Hospira, Inc., Lake Forest, IL (US)

Appl. No.: 13/358,609

Filed: Jan. 26, 2012

Related U.S. Application Data

Provisional application No. 61/437,047, filed on Jan. 28, 2011.

Publication Classification

Int. Cl.

A61B 8/04 (2006.01)

ABSTRACT

An ultrasonic monitoring device includes a substrate, a plurality of ultrasonic transducer elements, a computer readable memory medium, a microprocessor, and a power source. The ultrasonic transducer elements are coupled to the substrate. Each ultrasonic transducer element is separately configured to transmit a signal to a target area of a mammal and to receive an echo return signal from the target area. The computer readable memory medium includes program instructions. The microprocessor is coupled to the ultrasonic transducer elements and to the computer readable memory medium for executing the program instructions to determine a physiological parameter of the mammal based on a combined analysis of the echo return signals received by the ultrasonic transducer elements. The power source is coupled to at least one of the ultrasonic transducer elements, the computer readable memory medium, or the microprocessor for supplying electrical energy.

Appendix C: Information Leaflet
Patient Information Leaflet

Principal Investigator’s Name: Prof. G. O’Laghin

Project Title: Non-invasive Venous Pressure Measurement: Initial Calibration Study

Telephone No. of Principal Investigator: 353 (0)91 492685

You are being invited to take part in a clinical research study carried out at National University Ireland. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You are not obliged to take part in this study and choosing not to participate will have no adverse effect on your relationship to the university or its members.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision.

Why is this study being done?

Ambulatory Venous Pressure is a measurement that indicates the health of the veins in the lower limb. It has historically been done using a small needle to access a vein to measure pressure. This study will compare a non-invasive technique using ultrasound to the calculated pressures in the lower limb. (No needles are used in this study.)

The primary goal of this study is:

- To understand whether ultrasound-aided measurements can substitute for cannula venous pressure measurements.

You have been asked to participate as one of 12 healthy participants.
Who is organising and funding this study?

The team members involved in this work are

Prof. Gearoid O’Laighin - Head of Electrical & Electronic Engineering, NUIG and Principle Investigator for the project.

Paul Breen – Post-doctoral Researcher with Electrical & Electronic Engineering, School of Engineering and Informatics, NUI Galway

Barry Broderick – Post-doctoral Researcher with Electrical & Electronic Engineering, School of Engineering and Informatics, NUI Galway

Michael Kane – Post-graduate researcher with Electrical & Electronic Engineering, School of Engineering and Informatics, NUI Galway

How will it be carried out?

This study will commence in August, 2011 and will require only one visit from each participant. You have been asked to participate because you are aged 18 and over, are generally healthy, and are willing and capable of giving informed consent for participation in the study. You also do not have a history of venous disease, deep vein thrombosis, peripheral arterial disease or vertigo.

Procedures: What will happen to me if I agree to take part?

If you decide to take part in this study here is what will happen:

- You will be asked to come to the laboratory for a maximum period of 2 hours, at a time suitable to you.
- You will be asked to sign a consent form to say you agree to take part.
- If you decide to take part you are still free to withdraw at any time and without giving a reason.
- Initially a set of measurements will be taken including your height, your sternum height and length.
- You will be asked sit, stand, and recline while some ultrasound assisted measurements are taken some veins on your foot or near your ankle. These measurements will take only a few minutes each once they commence.
- A stability frame will be provided to aid in standing without swaying for a few minutes.
- These measurements consist of taking ultrasound images of your veins, while a small diaphragm pushes gently on the outside of your skin.
- These measurements will all be taken on the foot or the lower leg near the ankle.
• You will be asked to do heel raises (up on your toes) and then stand steadily for a minute or two whilst a surface measurement is taken from your foot or near your ankle.

Risks & Discomforts

A commercial Doppler Ultrasound device in concert with an adaptor having a mineral-oil filled diaphragm will be used throughout the study for vein cross-sectional measurements. The device will be used to take measurements of the blood vessels and venous pressure in your lower leg and foot. In order to do this a water based gel is spread on the top of the probe and the probe is held against the surface of your skin by an operator. The procedure will require you to expose your lower leg (below the knee) to allow adequate placement of the probe. These ultrasound measurements are widely used for a variety of purposes in clinical settings and pose no risk of discomfort or injury to you.

There are no foreseeable risks associated with taking part in this study. If however, any healthcare concerns are identified, we recommend that you contact your GP.

In the event of an adverse event, the following will happen: Emergency services will be called immediately, and you will receive appropriate medical treatment. We will also report the adverse event to the Research Ethics Committee, University Hospital Galway.

Benefits of this Study

There are no direct benefits for participants in this study. However, you will help us create a new way to measure pressure without discomfort. This may help create diagnostic options for patients without the trauma of needles.

Confidentiality

All information that is collected about you during the course of the research will be kept strictly confidential and will not be shared with anyone else. The information collected in this research study will be stored in a way that protects your identity. We will store the original data for 5 years after which it will be destroyed. Any information connecting you with this data will be destroyed upon study completion. Results from the study will be reported as group data and will not identify you in any way.

Your participation in this study is completely voluntary. If you do decide to take part you will be given this information sheet to keep and be asked to sign a
consent form. All information which is collected about you during the course of the research will be kept strictly confidential. You are free to withdraw from this study at any time and without giving a reason.

Project Duration

The project duration is 12 months. Your involvement is for one 2 hour session.

What if something goes wrong as a result of my participation in this study?
In the event of an adverse event the following will happen: Emergency services will be called immediately, the adverse event will be reported to the Research Ethics Committee, National University of Galway.

If you require further information

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be affected.

For additional information now or any future time please contact:

Name: Prof Gearoid O’Laighin
Address: Department of Electrical Engineering
NUI Galway
Galway

Phone No: 353 (0)91 492685
Email: gearoid.olaghan@nuigalway.ie

Alternately please call or email:

Michael Kane
353 (0)86 603 9800
001 651 253 9293
nomoran@visi.com

Appendix D: Consent Form

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CONSENT FORM

Project Title: Non-invasive Venous Pressure Measurement: Initial Calibration Study
Principal Investigator’s Name: Dr. Gearoid O’Leighin
Telephone No. of Principal Investigator: (0)91 492685

Please initial box

1. I am an adult taking part in this study between ages 18 and 65, inclusive.

2. I confirm that I have read and understand the information sheet for the above study and have been given a copy to keep. The information has been fully explained to me and I have been able to ask questions. I understand why the research is being done and any risks involved.

3. I understand that taking part in this research is voluntary and that I am free to withdraw at any time.

4. I am in good health, able to stand, sit, and lie for up to 10 minutes.

5. I do not have dizziness or vertigo.

6. I do not have a history of venous hypertension, venous ulcers, or deep vein thrombosis.

7. I do not have any open wounds on my foot or lower leg.

8. I also undertake to treat this study in a confidential manner, including all documentation, conversations, interventions and results.

9. I acknowledge the purpose of the study and any risks involved in the study procedures.

10. The nature and purpose of such procedures has been described to me in the Information Sheet.

11. I have been assured that information about me will be kept confidential.

12. I agree to take part in the above study.

Name of Participant ___________________________ Date ________________ Signature ___________________________

Name of Researcher ___________________________ Date ________________ Signature ___________________________

Appendix E: Healthy Patient Protocol
Study Protocol

Study Title: Non-invasive Venous Pressure Measurement: Initial Calibration Study

Project Description:
The venous pressure of the lower limb has been correlated to a number of socially significant circulatory disorders, among them chronic venous ulcers and deep vein thrombosis. The current standard of assessment relies heavily upon ultrasound imaging to provide anatomical data and insight into flow characteristics of the vascular network. However, pressure is directly linked to several of the pathologies of lower limb venous disease. Prior to the availability of ultrasound imaging, ambulatory Venous Pressure measurements were the gold standard diagnostic method. As a result of advances in ultrasound, it is a technique rarely practiced, and pressure data are not commonly collected.

The method of non-invasive pressure being investigated here follows similar work measuring central venous pressure described in the literature. This work was successful in that it had a good correlation to conventionally measured central venous pressure. The basic principle is that veins have very flaccid walls. When the pressure outside the vein exceeds the internal pressure, they close. This can be observed in real time using the ultrasound. This work differs as it has the potential to measure time-varying venous pressures that occur in the lower limb as a result of exercise and venous refilling processes. The venous refilling time and ambulatory venous pressure measurements may be rendered using this technique.

Objectives:
The primary objective of this study is to evaluate the utility and accuracy of a non-invasive venous pressure measurement approach using ultrasound imaging and an acoustically transparent bladder. The study will allow the comparison of the estimated static venous pressure in the lower limb with the calculated hemostatic pressure. It will provide a data set that will direct the calibration and the optimization of the technique.

Methodology:
Research Design:
12 Healthy volunteers will be recruited to allow for the evaluation of their static venous pressures in the lower leg and to observe their venous refilling time after 10 heel raise. The subject's height, sternal notch height, and sternal length will be measured to estimate the position of their right atrium. They will be asked to assume one of three postures and remain still for a few minutes in each posture. In each posture, the vertical distance between the vein observation site and the sternal notch will be measured. The postures include standing, sitting, and sitting with legs extended. In one phase of the study, they will be asked to stand and do 10 heel lifts within 30 seconds. In each case, after an appropriate stabilization interval, ultrasound images of the veins will be captured using the device.

The venous pressure test will gradually modulate a mineral oil filled diaphragm that is interposed between a commercial ultrasound imaging transducer and the surface of the limb over the vein. A short video capture will be obtained of the vein cross section as it responds to the surface pressure. This will be correlated with the instantaneous diaphragm pressure, the subject posture, and time.

- Patient Height
- Sternal length
- Sternal notch height
- Vein observation site to sternal notch vertical distance
- External diaphragm pressure
- Observation time and date
- Optional photographs of vein observation site

Exclusion Criteria - Potential participants will be excluded from the study in the following circumstances:
- Vertigo or dizziness
- A history of venous hypertension, venous ulcers, or deep vein thrombosis
- Any open wounds on the foot or lower leg

Inclusion Criteria – Participants must be:
- Over 18 years of age and in good health.
- Able to stand, sit, and lie for up to 10 minutes with the help of a stabilizing frame.
- Able to perform 10 heel raises within 30 seconds.

Criteria for Discontinuation – Participants will be immediately withdrawn from the study in the following circumstances:
- An expressed wish to discontinue.

Detailed Procedure -
**Screening:**
Subjects will be given the information sheet to review.
Subjects will be given an invitation to ask questions.
Subjects will be asked to read and sign the consent form.
Subjects will be given a random 3 character identifier used on all subsequent data files.

**Measurements:**
- A random number generator will be used to select the order of the postural measurements for the three static postures.

The researcher will identify an accessible vein in the lower limb (O).
The distances from the reference plane to each of the indicated sites will be recorded (O, H.S.X.).
The participant will be asked to remain still for between 1 and 2 minutes.
The researcher will observe the vein using the ultrasound imaging machine through the diaphragm whilst recording the instantaneous diaphragm pressure.

*Version 1.1 – 09/04/09*
The next posture in the sequence will be observed. After three postures have been observed and recorded, the participant will be asked to stand. An accessible vein will be identified and the participant will be asked to perform 10 heel rises. The vein diameter and instantaneous pressure will be recorded for approximately 1 minute.

Data Analysis
Ultrasound capture frames will be paired with instantaneous bladder pressure values as the veins transition from open to closed and back. These will be mapped to the calculated static pressures and to the tissue morphology.

Additional Notes:

References:

1. Nicolaidis, A. N. The value of dynamic venous-pressure measurements. WORLD JOURNAL OF SURGERY 10:919-924; 1986
Appendix F: Study Data Sheets

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<thead>
<tr>
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<tbody>
<tr>
<td>A1</td>
<td>Verify supplies on check sheet</td>
<td>1.0</td>
<td>2.0</td>
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<tr>
<td>A2</td>
<td>Start the laptop, ultrasound, and setup all programs to active mode</td>
<td>3.0</td>
<td>2.0</td>
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<tr>
<td>A3</td>
<td>Adjust the ultrasound to 12 mhz prob. 12mhz drive, B mode, gain 80, Edge enhancement 4, dynamic range 60, 1 focus point, focus position 1.75cm</td>
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<tr>
<td>A4</td>
<td>Have volunteer read information sheet</td>
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<td>A5</td>
<td>Ask volunteer to sign the consent form</td>
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<tr>
<td>A6</td>
<td>Assign 3 character random ID</td>
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<tr>
<td>A7</td>
<td>Create Excel data sheet in the VW1_Data.xls notebook. Name sheet by three letters</td>
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<tr>
<td>A8</td>
<td>Measure patient’s height &amp; Record</td>
<td></td>
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<tr>
<td>A9</td>
<td>Ask patient to permit sternum length measurement: Record</td>
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<tr>
<td>A10</td>
<td>Clean the Widget with IPA wipes on all surfaces</td>
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<tr>
<td>B1</td>
<td>Randomly select posture 1 (standing), posture 2 (seated, feet down), or posture 3 (seated feet extended)</td>
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<tr>
<td>B2</td>
<td>Press F9 to trigger Random number generation.</td>
<td>2.0</td>
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<td>B3</td>
<td>Note first posture on data sheet</td>
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<tr>
<td>B4</td>
<td>Ensure subject is positioned comfortably and stably</td>
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<tr>
<td>B5</td>
<td>Ask the patient if they have a leg preference</td>
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<tr>
<td>B6</td>
<td>Select the leg and note on information sheet</td>
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<tr>
<td>B7</td>
<td>Identify an accessible vein and verify a good image is possible.</td>
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<tr>
<td>B8</td>
<td>Note the location of the vein</td>
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<tr>
<td>C1</td>
<td>Measure floor to vein distance and record</td>
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<tr>
<td>C2</td>
<td>Measure floor to suprasternal notch distance and record</td>
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<tr>
<td>C3</td>
<td>Let the VW operate for a moment on the subject’s skin; answer any questions.</td>
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<td>C4</td>
<td>Ask the patient to stay relaxed, still their legs, and avoid talking for the next few minutes of data collection</td>
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<tr>
<td>C5</td>
<td>Collect on video unloaded of the membrane travel and pressure, 10 sec slow speed. Name XYZ Cal</td>
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<tr>
<td>C6</td>
<td>while waiting, create the data file for the xyz trench (SFD, SFExt, STD, STDHR)</td>
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<tr>
<td>C7</td>
<td>Position the VW on the vein and verify a good trench image</td>
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<tr>
<td>C8</td>
<td>Start the video collection software</td>
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<tr>
<td>C9</td>
<td>Start the VW: Slow ramp: ~20 s; Fast ~10s; Vslow ~20Sec</td>
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<tr>
<td>C10</td>
<td>Stop the video collection: Check video is intact.</td>
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<tr>
<td>C11</td>
<td>Let the patient relax and ask questions</td>
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<tr>
<td>C12</td>
<td>Tell the patient another collection will occur.</td>
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<tr>
<td>C13</td>
<td>Ask the patient to stay relaxed, still their legs, and avoid talking for the next few minutes of data collection</td>
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<tr>
<td>C14</td>
<td>Wait 45 seconds before collecting data</td>
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<tr>
<td>C15</td>
<td>while waiting, create the data file for the xyz cross (SFD, SFExt, STD, STDHR)</td>
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<tr>
<td>C16</td>
<td>Position the VW on the vein and verify a good cross image</td>
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<td>C17</td>
<td>Start the video collection software</td>
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<tr>
<td>C18</td>
<td>Start the VW: Slow ramp: ~20 s; Fast ~10s; Vslow ~20Sec</td>
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<tr>
<td>C19</td>
<td>Stop the video collection</td>
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</tr>
<tr>
<td>C20</td>
<td>Let the patient relax and ask questions</td>
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Works Cited


