Neuro-Muscular Electrical Stimulation for the Treatment of Orthostatic Hypotension in an Older Community Dwelling Population

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Declaration

I hereby declare that the work contained in this thesis is my own, and was completed with counsel of my supervisors Professor Declan Lyons and Professor Colum Dunne. This work has not been submitted to any other University or higher education institution, or for any other academic award in this University.

Where the work of others has been reported, it has been fully acknowledged and referenced.

__________________
Colin Quinn
Abstract

Orthostatic hypotension (OH) is highly prevalent in older people and is associated with increased morbidity and mortality. Current treatment options include pharmacological and non-pharmacological approaches, although robust evidence regarding therapeutic efficacy is lacking. The overarching aim of this thesis is to investigate the potential benefit of neuromuscular electrical stimulation (NMES) in attenuating blood pressure (BP) reductions in community dwelling older subjects with OH. The first study incorporated two surveys to evaluate patient and physician practices and perceptions of using elastic compression stockings (ECS), which are currently frequently used for this indication. This study found that only one third of patients wear ECS daily, with practical difficulties limiting their use specifically in an older age group. The physician survey concluded that although ECS are prescribed frequently, there is significant discrepancy between physician prediction of patient compliance, and actual patient compliance which may reflect the current lack of convincing evidence regarding their efficacy. The second study incorporated a randomised crossover design investigating the use of both simultaneous and alternate leg calf muscle NMES during head-up tilt table testing. In this feasibility study, a trend toward benefit was demonstrated with alternate leg NMES setting. The third study evaluated the effect of both alternate and simultaneous NMES in a young, healthy population during head-up tilting and demonstrated a more favourable haemodynamic response and tolerability profile with alternate NMES. The final study compared the effect of alternate leg calf muscle NMES and ECS during both passive and active orthostatic challenges. Both NMES and ECS significantly attenuated BP reductions during orthostasis in comparison to control, with NMES resulting in significantly higher venous blood flow responses and demonstrated to be tolerable. There was no significant difference in systolic or diastolic BP between NMES and ECS interventions. In conclusion, NMES has been demonstrated to be as effective as ECS in attenuating BP reductions in an older subject group with OH during active and passive orthostatic challenges and is tolerable. Future study should evaluate the longer term efficacy and practicality of NMES for this indication.
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Chapter 9 Discussion and Conclusion

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List of Abbreviations

**Anatomy:**
- ANS: autonomic nervous system
- AP: action potential
- CMP: calf muscle pump
- EPSP: excitatory post synaptic potential
- nAChR: nicotinic acetylcholine receptor
- NMJ: neuromuscular junction
- RAAS: renin angiotensin system
- PNS: parasympathetic nervous system
- SNS: sympathetic nervous system

**Equipment:**
- ECS: elastic compression stockings
- ES: electrical stimulation
- FES: functional electrical stimulation
- IPC: intermittent pneumatic compression
- NMES: neuro-muscular electrical stimulation
- TENS: trans-cutaneous electrical stimulation
- VAS: visual analogue scale

**Hemodynamics:**
- BP: blood pressure
- CA: cerebral autoregulation
- CBF: cerebral blood flow
- CO: cardiac output
- DBP: diastolic blood pressure
- HR: heart rate
- MAP: mean arterial pressure
- PSV: peak systolic velocity
- SBP: systolic blood pressure
- SV: stroke volume
- TPR: total peripheral resistance
- VFV: venous flow volume

**Medical conditions and definitions:**
- ANF: autonomic failure
- CI: cognitive impairment
- CCF: congestive heart failure
- CHD: coronary heart disease
- COH: consensus orthostatic hypotension
- DVT: deep venous thrombosis
- EPO: recombinant erythropoietin
- IOH: initial orthostatic hypotension
- MSA: multiple systems atrophy
- OH: orthostatic hypotension
- OI: orthostatic intolerance
PAF pure autonomic failure
POTS postural orthostatic tachycardia syndrome
SCI spinal cord injury

**Medications:**
L-DOPS L-dihydroxyphenylserine (droxidopa)

**Physiological measurement:**
AS active stand
ECG electrocardiogram
EMG electromyography
HUT head upright tilt

**Units of measurement:**
bpm beats per minute
cm.s\(^{-1}\) centimetres per second
Hb haemoglobin
Hz hertz
I current
MCV muscle conduction velocity
MHz megahertz
mmHg millimetres of mercury
R resistance
V voltage

**Treatment:**
SHU sleeping in the head-up position
Chapter 1

Introduction
1.1. Background and Rationale for Thesis

Syncope can be defined as “transient loss of consciousness due to global cerebral hypoperfusion, characterised by rapid onset, short duration and complete spontaneous recovery” (Moya et al. 2009), and accounts for 1-3% of all unselected emergency presentations to secondary care (Day et al. 1982; Greve et al. 2014; Matthews et al. 2014). The annual incidence of syncope in the elderly is 6-10% (Lipsitz et al. 1985; Rafanelli et al. 2014), increasing with age (Soteriades et al. 2002). Syncope is associated with significant resultant trauma and disability (Kapoor et al. 1986) and increased mortality in older people (Ungar et al. 2011). The economic burden of unnecessary investigations in an older patient group presenting to the emergency services with syncope is significant (Johnson et al. 2014), and has been estimated at $16000 per patient, which does not take into account costs of inpatient stay and continuing care (Calkins et al. 1993).

Syncope can be classified as neurally-mediated, of cardiac origin, or syncope due to orthostatic hypotension (OH) (Moya et al. 2009). Neurally-mediated causes include vasovagal syncope which is more common in a younger age group and can frequently be precipitated by emotional stress or hypovolaemia. Situational syncope is characterised by an exaggerated autonomic reflex which may occur for example during straining, or carotid sinus syncope which is associated with carotid sinus hypersensitivity. Cardiac causes of syncope can be associated with arrhythmia or structural disease and are more common as age progresses.

OH is found in up to 31% of patients presenting with syncope (Atkins et al. 1991) and is associated with primary or secondary autonomic failure, pharmacological agents or volume depletion. The prevalence OH increases with age (Benvenuto and Krakoff 2011) and is proven to be linked with increased mortality and morbidity in this population (Angelousi et al. 2014). Current therapeutic strategies for managing OH involve non-pharmacological and pharmacological measures. These strategies are currently often suboptimal with limited robust evidence available in the literature regarding their efficacy (Logan and Witham 2012).
Neuromuscular Electrical Stimulation (NMES) is defined as the application of an electrical stimulus to motor points in the body using electrodes placed on the surface of the skin in order to elicit muscular contraction (Doucet et al. 2012). NMES has been widely used in the rehabilitation setting to enhance motor function and more recently developed as a blood flow assist device when applied to the calf muscles (Lyons et al. 2002; Clarke Moloney et al. 2006). NMES has been demonstrated to improve orthostatic blood pressure (BP) reductions and symptoms when applied to the lower limbs of patients with autonomic dysfunction following spinal cord injury (Faghri et al. 1992; Sampson et al. 2000; Yeh et al. 2010).

1.2. Aim of Thesis

The overarching aim of this thesis is to investigate the potential benefit of NMES as a non-pharmacological therapeutic measure in attenuating BP reductions in community dwelling older people with proven OH.

1.3. Structure of Thesis

The thesis is composed of nine chapters which can be summarised as follows:

Chapter Two:

This chapter reviews our current understanding of OH, outlining current and historic definitions, epidemiology, pathophysiology, clinical relevance and management strategies, highlighting limitations in the current available evidence.

Chapter Three:

Chapter three reviews the normal physiology of muscle contraction, basic principles and components of NMES, the effects on skeletal muscle followed by a review of the clinical applications currently used.
Chapter Four:

The subject recruitment and general methodology employed in the clinical research studies in chapters six to eight are discussed in chapter four.

Chapter Five:

*Hypothesis:* Elastic compression stockings (ECS) are commonly used in an older patient group with OH. It was hypothesised that their frequent use may be limited by practical issues.

*Aims:* To explore the potential factors relating to patient compliance and to identify current specialist physician prescribing practices when using ECS.

Chapter Six:

*Hypothesis:* NMES of the calf muscles will result in favourable haemodynamic effects in an older, community dwelling cohort of subjects with OH undergoing passive orthostatic challenge.

*Aims:* To determine the haemodynamic effect of calf muscle NMES in this subject group and also to identify the optimal NMES stimulation pattern.

Chapter Seven:

*Hypothesis:* Calf muscle NMES will be well tolerated in a young, healthy cohort undergoing passive orthostatic challenge.

*Aims:* To objectively evaluate subject tolerance to NMES and its effect on symptoms. A secondary objective is to assess the haemodynamic effect of NMES using objective measures of venous blood flow.
Chapter Eight:

Hypothesis: Calf muscle NMES will result in favourable haemodynamic effects in a healthy older, community dwelling cohort of older subjects with OH during passive and active orthostatic challenges.

Aims: To compare the haemodynamic effects of calf muscle NMES and lower limb ECS in this group using different orthostatic stressors. A secondary objective was to assess subject tolerability and effect on symptoms incorporating objective measures of lower limb venous blood flow.

Chapter Nine:

The final chapter summarises the findings of the clinical research studies presented, their contribution to the literature, limitations, followed by a discussion of potential future research.
Chapter 2
Orthostatic Hypotension Literature Review
2.1. Definitions and Classification of Orthostatic Hypotension

2.1.1. Consensus OH

Orthostatic Hypotension (OH) was defined in 1996 by an expert panel convened to generate consensus on the definitions of OH, pure autonomic failure (PAF), and multiple system atrophy (MSA):

“Orthostatic hypotension is a reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing. It is a physical sign and not a disease. An acceptable alternative to standing is the demonstration of a similar drop in blood pressure using a tilt table in the head-up position, at an angle of at least 60 degrees. OH may be symptomatic or asymptomatic. Symptoms of OH are those that develop on assuming the erect posture following head-up tilt, and usually resolve on resuming the recumbent position.”.

(Kaufmann 1996)

At this time, the widely accepted diagnostic modality for OH was conventional sphygmomanometry. Over recent years, more accurate technology for the identification of OH has been developed and has progressed considerably (Imholz et al. 1998) with the advent of continuous, non-invasive, beat-to-beat plethysmography technology (Finapres). This has been increasingly used for the diagnostic assessment of OH and has resulted in modifications to this definition reflecting recent advances in the understanding of OH.

2.1.2. Updates to the Consensus Definition

The European Society of Cardiology guidelines for the management of syncope were updated in 2004 (Brignole, Alboni, Benditt, Bergfeldt, Blanc, Bloch Thomsen, et al. 2004) with the most recent release in 2009 (Moya et al. 2009). This outlined the definition and characteristics of three main distinct OH syndromes in older people as classical, initial and delayed, using continuous non-invasive BP measurements:

“Classical OH is a physical sign defined as a decrease in systolic BP > 20 mmHg and in diastolic BP of > 10 mmHg within three minutes of standing, described in patients with pure autonomic failure, hypovolaemia, or other forms of autonomic failure.
Initial OH is characterised by a BP decrease immediately on standing of > 40 mmHg, BP the spontaneously and rapidly returns to normal, so the period of hypotension is short (<30 s).

Delayed (progressive) OH is not uncommon in elderly persons. It is attributable to age-related impairment of compensatory reflexes and stiffer hearts in the elderly sensitive to decreased preload. Delayed OH is characterised by a slow, progressive decrease in systolic BP on assuming the erect posture. The absence of a bradycardic reflex (vagal) differentiates delayed OH from reflex syncope. Delayed OH, may, however, be followed by reflex bradycardia, where, in the elderly the fall in BP is less steep than in the young”.

(Moya et al. 2009)

IOH can only be diagnosed with Finapres technology during active standing and is not identifiable during HUT due to a lack of the vasodilatatory reflex associated with lower limb skeletal muscle activation which is not seen during passive orthostatic challenge. IOH is thought to account for 3-4% of syncope cases presenting for medical assessment (Wieling et al. 2007). Delayed OH has been found in up to 39% of patients beyond ten minutes of head-up tilting, and it is suggested that this may be a mild or early form of sympathetic failure (Gibbons and Freeman 2006).

An update to the consensus statement on the diagnosis of neurally-mediated OH was released in 2011 which described OH:

“a sustained reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 min of standing or head-up to at least 60° on a tilt table. It is also suggested that, in patients with supine hypertension, a reduction in SBP of 30 mmHg may be more accurate for the diagnosis of OH”.

(Freeman et al. 2011)

The duration of the sustained reduction in BP remains unclear which leaves uncertainty for clinicians using modern measures of orthostatic blood pressure (BP) decay.

2.1.3. Morphological Classification

Recent developments have included the identification of three different morphological response patterns of BP decay following orthostasis using Finometer technology (Romero-Ortuno, Cogan, Foran, et al. 2011). The normal, or quick
recovery pattern following orthostasis is frequently seen and is not associated with comorbidity. The slow recovery pattern can be seen in patients with vasodepressor carotid sinus hypersensitivity (Kerr et al. 2006; Tan et al. 2008), and the failure to recover pattern, seen in patients with autonomic failure (ANF) (Wieling and van Lieshout 1993).

It is presently unclear as to the clinical significance of these morphological patterns (Romero-Ortuno, Cogan, Foran, et al. 2011; Cooke et al. 2013), however medications such as antidepressants and beta blockers have been found to be an independent predictor of the failure to recover pattern which is thought to be the most pathological (Romero-Ortuno et al. 2013). It has been suggested that these patterns could be included in future research to predict adverse outcome of OH.

2.2. Orthostatic Intolerance

Orthostatic intolerance (OI) is defined as the inability to tolerate the upright posture due to a circulatory abnormality which is relieved by recumbence (Shibao, Lipsitz, et al. 2013). Symptoms of chronic OI are frequently reported by patients with both OH and another disorder of orthostasis, postural orthostatic tachycardia syndrome (POTS) which is more common in younger persons (Robertson 1999; Freeman et al. 2011). Signs and symptoms of OI are numerous and may include transient loss of consciousness (syncope), visual and hearing disturbances, light-headedness, dizziness, headache, fatigue, weakness, nausea, abdominal and neck pain, sweating, and tremulousness (Freeman 2008; Moya et al. 2009). Of these, syncope or severe light-headedness are the most likely to directly provoke recumbence or lead to seek medical attention. OI is common in the general population with most people experiencing some degree of symptoms associated with OI during their lives, if only transiently during periods of hypovolaemia (Ocon, Medow, et al. 2009).
2.3. Epidemiology of OH

The prevalence of OH in community dwelling older subjects increases with age and is reported between 5% and 34% (Rutan et al. 1992; Low and Singer 2008; Hiitola et al. 2009; Benvenuto and Krakoff 2011), see Figure 2-1. These studies used traditional sphygmomanometry or automated oscillometry to diagnose OH. More recently, using Finometer technology which is more sensitive in identifying OH, the prevalence of OH in otherwise healthy community dwelling adults was reported to be as high as 58% (Cooke et al. 2013).

Using sphygmomanometry, the prevalence of OH in 295 older subjects with hypertension attending primary care clinics was found to be 14.6%, with one in four of these patients describing symptoms of OI (Vara González et al. 2001). Using the same assessment method, OH was demonstrated in 24% of 788 patients presenting to an emergency department with syncope (Sarasin et al. 2002). Over half (55%), of 505 patients attending geriatric outpatient clinics fulfilled the diagnostic criteria for OH with 35% of those taking at least one vasoactive medication that has been shown to contribute to OH (Poon and Braun 2005). In a Dutch study of eighty five patients admitted to an acute geriatric department, diagnostic OH was present in 52% using an automated BP cuff (Vloet et al. 2005). OH has been demonstrated in 20-50% of nursing home residents (Palmer 1983; Ooi et al. 2000; Iwanczyk et al. 2006).
Figure 2-1: Prevalence of OH increases with age. Combined data from the ARIC and CHS studies adapted from (Benvenuto and Krakoff 2011)
2.4. Normal Control of Blood Pressure During Orthostasis

Orthostatic integrity requires efficient independent function of neurovascular compensation, neuro-humoral effects, cerebral blood flow regulation and lower limb skeletal muscle pump (Freeman 2008). In order to maintain a stable BP following assumption of the upright posture, several key regulatory mechanisms must operate simultaneously. An adequate blood volume is necessary with the integration of several reflex and humoral systems to maintain stable BP on standing. The autonomic control of BP following standing is predominantly mediated by the vasomotor centre in the brainstem with pathways to the carotid baroreceptors, cardiac ganglion and skeletal muscle (Sjostrand 1952). A number of key centres have been identified, which can be summarised as follows and illustrated in Figures 2-2 and 2-3. A collection of neurons responsible for sympathetic activation and vasoconstriction are located bilaterally in the anterolateral portions of the upper medulla, with the vasodilator area found in the anterolateral portions of the lower half of the medulla. The nerve fibres originating in this area are connected to the vasoconstrictor area, and inhibit sympathetic activity in this area, thereby facilitating vasodilation.

A sensory region is located in the nucleus tractus solitarius of the posterolateral portions of the upper medulla and upper pons. The neurons in this location receive input from baroreceptors located in the aortic arch and carotid sinuses via the vagus and glossopharyngeal nerves respectively, and output signals to control the activities of the vasoconstrictor and vasodilator areas (Such 1971). This circulatory reflex control system is known as the baroreflex, which acts as short-term BP regulatory mechanism. The normal orthostatic control of BP involves immediate and delayed responses which will be discussed separately.
Figure 2-2: Overview of the anatomy of the autonomic system
Figure 2-3: Location of baroreceptors in carotid sinus and arch. Left: Location of baroreceptors in carotid sinus and aortic arch. Right: Effects of arterial firing with increasing arterial pressure increasing carotid firing rate. Maximal baroreceptor sensitivity occurs near normal mean arterial pressure.
2.4.1. Immediate Response to Orthostasis

Pooling of venous blood in the legs and abdomen begins almost immediately upon assuming the upright posture. It is estimated that between 500-800 ml of thoracic blood can be transferred to the regions below the diaphragm (Sjostrand 1952; Self et al. 1996). The result of this blood volume redistribution is reduced venous return to the heart with subsequent fall in central venous pressure associated with a decrease in cardiac filling, stroke volume (SV) and cardiac output (CO) (Smit et al. 1999). The autonomic nervous system (ANS) mediates short term adjustments to orthostasis by resulting in increased total peripheral resistance (TPR) and heart rate (HR). Initially, reduced stretch and inactivation (unloading) of the inhibitory arterial baroreflexes contribute to the immediate restoration of venous return and subsequently BP. This leads to sympathetic vasoconstriction and venoconstriction within the splanchnic circulation resulting in increased venous return to the heart. Afterward both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are usually slightly increased compared with the supine position (Wieling and Shepherd 1992) with stabilisation normally achieved within 30-60 seconds.

2.4.2. Delayed Response to Orthostasis

After several minutes of sustained orthostasis, microvascular filtration from plasma to interstitium continues. Partial restoration of blood volume depends on lymphatic activity and reabsorption of interstitial fluid into the blood volume which is facilitated by activation of the skeletal muscle pump (Victor and Mark 1985; Huxley and Scallan 2011). As discussed, orthostatic stabilisation is usually achieved within one minute of standing. In the longer term, the rennin-angiotensin system (RAAS), as well as the activities of skeletal muscles and those of respiration help maintain stable BP. The RAAS generally only becomes active after several minutes of hypotension. Decreased arterial pressure and sodium chloride levels of the ultrafiltrate of the nephron are detected by the juxta-glomerular process kidney which increases renin production (Kobori et al. 2007). Renin hydrolyses Angiotensinogen to Angiotensin I that is subsequently converted in the lung to Angiotensin II. This in turn has the dual effect of increasing TPR by causing peripheral vasoconstriction and
CO by increasing renal retention of salt and water, which results in an increase in systemic BP.

2.5. Cerebral Autoregulation

CNS symptoms of OI have been demonstrated to be related to a decrease in cerebral blood flow (CBF) (Ocon, Kulesa, et al. 2009). Reduction of CBF as a result of orthostasis may result in transient impairment of cerebral autoregulation (CA) indicating that CBF is no longer independent of perfusion pressure. CA is a key defence mechanism against syncope and is an intrinsic mechanism of the cerebrovasculature that maintains CBF relatively constant over a wide range of BP between 60 to 150 mmHg (Gardner and Lee 2007), see Figure 2-4. These limits are not fixed however, and are dependent on individual differences between subjects and the effects of various pathologies. In healthy individuals, CBF is relatively independent of sympathetic influences except during very rapid changes and extremes of BP (Hamner et al. 2010). Symptomatic OH occurs when SBP falls below the range of efficient CA, resulting in cerebral hypoperfusion and consequent symptoms of OI.

CBF has been shown to be reduced by hypocapnia, which can accompany OI (Lagi et al. 2001; Stewart et al. 2006). In a study of twenty one individuals with ANF, it was shown that CA is variable in this group with three patterns demonstrated:

“The most common patterns of cerebral response to OH are autoregulatory failure with a flat flow-pressure relationship, or intact autoregulation with an expanded autoregulated range. The least common pattern is autoregulatory failure with a steep flow-pressure relationship”.

(Novak et al. 1998)

Patients with the first two patterns have an enhanced capacity to cope with OH, while those with the third, reduced capacity. It has been demonstrated in a study of 554 older subjects that women can maintain CBF more effectively than men during postural change (Deegan et al. 2011), with older women also found to tolerate prolonged orthostatic stress better than men volunteers (Mellingsæter et al. 2013),
which may in some way explain why there is a higher prevalence of symptomatic OH in older men.

Figure 2-4: Theoretical shifts in cerebral autoregulatory curve (Serrador et al. 2001)
2.6. Calf muscle pump

The muscle pumps of the calf and foot complement the BP stabilisation mechanisms outlined above by providing the motive force for venous return against gravity when activated on standing. The inflow of blood to a segment of deep vein is through intake valves from perforating veins as well as from the deep vein segment below. Blood flows through an outflow valve to the deep vein segment above with these valves effective in preventing reflux of blood to the segment below (Falanga and Eaglstein 1993; Orsted et al. 2001), see Figure 1-5. The main muscles of the leg that affect the calf muscle pump (CMP) include gastrocnemius and soleus. Contraction of these muscles compresses the intramuscular and deep veins, propelling blood in the deep venous system to flow toward the heart.

For efficient CMP function, adequate ankle joint mobility and proficiency of the deep veins are necessary (Orsted et al. 2001). The CMP is composed of several pumps in the leg from the foot to the upper thigh which synchronise during walking resulting in efficient return of venous blood to the iliac veins and subsequently right atrium (Styf 1990; Gardner and Fox 1992). The distal CMP is emptied by dorsiflexion of the foot before weight-bearing. Weight-bearing on either foot empties the foot pump; and plantar flexion following weight-bearing empties the proximal CMP to upward venous blood flow proximally to the heart. In the absence of pathology, this system functions to reduce lower limb venous pressure from nearly 100 mmHg to 22 mmHg within several steps (Meissner et al. 2007).
Figure 2-5: Calf muscle pump. As the muscles of the lower leg contract the blood in the veins is pushed upwards towards the heart. The valves in the veins are opened by the pressure of blood moving upwards. When the muscles relax, the valves close preventing backflow and pooling of blood.
As mentioned earlier, prolonged orthostasis results in increased microvascular filtration of fluid from the capillaries into the dependent tissues. This can result in a 20% or greater decrease in plasma volume, even in young healthy people (Hagan et al. 1978). To counteract this, prolonged orthostatic stress is associated with increased muscle sympathetic nerve activity (Joyner et al. 1990). These regulatory responses stimulate vessel constriction and increased muscle tone, which in healthy individuals serves to maintain or even increase BP when upright. The tonic activity of the soleus muscle is particularly important in this process because it serves both as the primary means for maintaining upright stance and the primary lower leg muscle pump, which returns venous and lymphatic fluid from the dependent tissues back to the circulatory system.

Earlier studies investigating the effect of the stimulation of postural reflex pathways have shown that CMP activity can be enhanced artificially, thereby assisting in the maintenance of BP during orthostasis (Inglis et al. 2002; Madhavan et al. 2005). Stimulation of the CMP can be achieved through mechanical stimulation of the plantar surface, which activates the cutaneous mechanoreceptors used in postural maintenance (Inglis et al. 2002). Plethysmographic techniques have been used to show that reflex-mediated CMP stimulation approximately doubles the lymphatic return pressure in the leg (Stewart et al. 2005). A study incorporating cardiovascular monitoring has shown that plantar stimulation is capable of limiting the acute BP drop associated with orthostasis (Madhavan et al. 2005). Another study evaluated the effects of plantar-based micro mechanical stimulation on delayed BP decreases in thirty healthy adult women during quiet sitting (Madhavan et al. 2008). Almost 25% of participants demonstrated findings consistent with delayed OH with significantly less reductions in SBP and DBP in the CMP stimulated group, concluding that delayed OH in healthy individuals may be precipitated by inadequate calf muscle tone.

Intermittent pneumatic compression (IPC) actively compresses the lower leg, mimicking the action of the leg muscle pumps. IPC has been demonstrated to reduce venous stasis and increases flow velocity resulting in favourable haemodynamic changes such as venous pressure and interstitial oedema (Chen et al. 2001; Kumar et al. 2002). Clinical applications of IPC include chronic venous insufficiency
including venous ulceration and more recently DVT prophylaxis in patients following stroke (Rowland 2000; Kumar et al. 2002; Dennis et al. 2013). Interestingly, a recent case report has highlighted the potential effect of IPC in stabilising BP and symptoms of OI in a patient with traumatic thoracic spinal cord injury (Helmi et al. 2013), although there are currently no controlled trials in the literature investigating its potential for this indication.

### 2.7. Causes of OH

#### 2.7.1. Introduction

OH can be caused by failure in one or more of the mechanisms as outlined which function simultaneously to maintain BP following orthostasis. The normal ageing process is associated with impairments of cerebral autoregulation (Wollner et al. 1979), baroreflex sensitivity (Wahbha et al. 1989), intravascular volume regulation (el-Sayed and Hainsworth 1995) and neuro-humoral control (Minaker et al. 1991). These changes, in combination with diminished cardiac-autonomic modulation (Barantke et al. 2008), reduce the efficiency of the compensatory mechanism to maintain BP following orthostasis. It is important to distinguish between neurogenic and non-neurogenic causes of OH, as therapeutic strategies are somewhat different. Neurogenic causes mainly involve central nervous system (CNS) degenerative processes that result in central or peripheral autonomic nervous system (ANS) dysfunction with consequent orthostatic instability. Non-neurogenic causes of OH may be related to decreases in effective blood volume or cardiac pump failure and will require different therapeutic considerations.

#### 2.7.2. Neurological causes

In patients with autonomic failure (ANF), OH occurs due to an impaired ability to increase vascular resistance upon assuming the upright posture. The neurological diseases with the highest prevalence of neurogenic OH are PAF, MSA, diabetic autonomic neuropathy, auto-immune autonomic neuropathy and paraneoplastic autonomic neuropathies (Kaufmann 1996; Grubb et al. 2003; Freeman 2008). PAF is an idiopathic, neurodegenerative disorder, characterised by OH, and with evidence
of more widespread autonomic failure (e.g. disturbed bladder, bowel, sudomotor and sexual function). Reduced supine plasma norepinephrine levels have been demonstrated in PAF with widespread distribution of Lewy bodies in peripheral pre and post synaptic neurons resulting in impaired signal transmission (Kaufmann et al. 2001). Symptom onset usually begins during middle age with men more frequently affected than women. The onset of PAF is usually slow and insidious, with mild symptoms often concealed for years by compensatory mechanisms, followed by a progressive stage of deteriorating autonomic function and associated symptoms.

MSA is characterised by a triad of central autonomic dysfunction, parkinsonism, and ataxia which usually manifests after the age of 50 years. Plasma noradrenaline levels are generally normal in MSA with intact baroreflex responses which contrasts to those found in both PAF and Parkinson’s disease (Goldstein et al. 1989). As in PAF, pre-syncope and syncope are the symptoms most likely to cause the patient see a physician. Some may present with “akinetic-rigid” syndrome that can be difficult to distinguish from Parkinson’s disease and may be classified as Parkinson plus syndrome following initial presentation. Idiopathic Parkinson’s disease is a common neurodegenerative disorder that is associated with increasing age. Up to 30% of patients with idiopathic Parkinson’s disease may also present with associated with progressive autonomic dysfunction and a predisposition to OH and falls (Velseboer et al. 2011), complicating its pharmacological therapy with medications that may result in vasoactive side effects.

2.7.3. Non-neurological causes

OH can be caused by a wide number of other factors, including hypovolaemia, cardiac disease, malignancies, chronic renal failure, and hypoadrenalism (Mathias 1995). Tables 1.1 and 1.2 summarise the most frequent medical conditions and medications that can contribute to OH.
### Table 2-1: Medical causes of non-neurogenic OH (Mathias 1995)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolaemia</td>
<td>Dehydration, blood loss, adrenal insufficiency, diarrhoea, diabetes insipidus</td>
</tr>
<tr>
<td>Cardiac Impairment</td>
<td>Bradycardia, Aortic or mitral valve dysfunction, tachyarrhythmia, myocardial infarction, pericarditis, acute or chronic heart failure</td>
</tr>
<tr>
<td>Vasodilation (venous pooling)</td>
<td>Prolonged recumbency or standing, fever, post-prandial dilation of splanchnic vessels, severe venous varicosities</td>
</tr>
</tbody>
</table>

### Table 2-2: Medications that can commonly contribute to OH (Schoenberger 1991; Poon and Braun 2005)

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1-agonists</td>
<td>Doxazosin, tamsulosin, prazosin, terazosin</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>ACE inhibitors, beta blockers, clonidine, nitrates, alpha blockers</td>
</tr>
<tr>
<td>Opioids</td>
<td>Morphine, tramadol, oxycodone</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Loop diuretics, hydrochlorothiazide</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Tricyclic antidepressants, trazadone, monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Phosphodiesterase type 5 inhibitors</td>
<td>Sildenafil, vardenafil</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Sinemet, madopar</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Pramipexole, ropinorole</td>
</tr>
</tbody>
</table>
2.8. Clinical Associations of Orthostatic Hypotension

2.8.1. Mortality

Several longitudinal studies using conventional sphygmomanometry for the diagnosis of OH have reported on the potential adverse associations of OH over the past fifteen years. The Honolulu Heart Project was a prospective study of cardiovascular disease in 3,522 older men followed up over four years (Masaki et al. 1998). In this cohort, OH was independently predictive of all-cause mortality with hazard ratio 1.64. This study demonstrated a linear association between orthostatic change in SBP and 4-year mortality rates. In another prospective study, diastolic OH at one minute and systolic OH at three minutes was shown to predict vascular death in 792 community dwelling older persons (Luukinen et al. 1999). Atherosclerosis Risk in Communities (ARIC) was a prospective study of 12433 community dwelling subjects with follow up over six years (Rose et al. 2000) which found an association between OH and a higher risk of coronary heart disease (CHD) after controlling for age, ethnicity, comorbid conditions and cardiovascular risk factors. A follow up study of ARIC (Rose et al. 2006) confirmed OH as an independent risk factor for all-cause mortality after adjustment for cardiovascular risk factors, hazard ratio 2.0.

Another epidemiological study performed in Rotterdam was a population-based prospective study of nearly 8,000 older adults with an average age of 68 years (Verwoert et al. 2008). This study found OH to be predictive of CHD and all-cause mortality over a 6-year follow-up period. The Malmo Preventative Project investigators studied the association between OH and vascular mortality (Fedorowski et al. 2010a) with follow-up extended for an average of 22.7 years. It reported a significant increase in the risk of all-cause mortality and coronary events in the OH group (Fedorowski et al. 2010b). In an Irish longitudinal study of 4415 participants, it has been suggested that higher orthostatic HR may also be an independent predictor of mortality (Romero-Ortuno et al. 2014). A recent systematic review of 28 prospective studies concluded that OH is predictive of all-cause mortality, hazard ratio 1.36 (Angelousi et al. 2014).
2.8.2. Hypertension and Systolic-Hypertension Syndrome

The association of arterial hypertension and OH has been well established using traditional sphygmomanometry to confirm the diagnosis (London et al. 1988; Beckett et al. 1999; Biaggioni and Robertson 2002; Shin et al. 2004; Fedorowski et al. 2009). OH is considered to be a form of pre-hypertension in younger, normotensive adults (Kario 2013), while using 24-hour ambulatory BP monitoring, OH has been found to be associated with an abnormal BP profile of reversal of circadian pattern (i.e. nocturnal hypertension, non-dipping), postprandial hypotension, and non-compensatory heart rate variability (Campbell et al. 1975; Carmona et al. 2003; Ejaz et al. 2004, 2007; Kazory et al. 2007; Ali et al. 2010). OH is two to three times more prevalent in reverse dippers than non-dippers (Fagard and De Cort 2010) and is predictive of cardiovascular events.

The syndrome of supine hypertension and orthostatic hypotension (SH-OH) poses a particularly difficult therapeutic challenge as treatment of one aspect of the condition may adversely affect the other (Naschitz et al. 2006). There are no longitudinal studies examining the clinical significance of SH-OH, however, several cross-sectional studies have found that patients with ANF and SHOH develop early cardiac or renal end-organ damage (Vagaonescu et al. 2000; Maule et al. 2006). There is also a positive association between the severity of supine hypertension and that of OH with lower levels of peripheral noradrenaline found, indicating the possible involvement of pressor mechanisms independent of the sympathetic system (Goldstein et al. 2003). As BP is traditionally tested while sitting up, supine hypertension may remain largely undetected for prolonged periods, until eventually presenting with symptoms of end-organ damage.

2.8.3. Cardiovascular and Cerebrovascular Disease

OH has recently been proposed as an independent haemodynamic cardiovascular risk factor for cardiovascular and cerebrovascular disease as it is associated with hypertensive target organ damage (Kario 2013). OH has been demonstrated to be associated with congestive cardiac failure in several cross-sectional studies (Kassis 1987; Potocka-Plazak and Plazak 2001). In the ARIC study, subjects with OH had an
increased risk of coronary heart disease, hazard ratio 1.85. (Rose et al. 2000). A DBP drop immediately after standing in older subjects has been demonstrated to be associated with a high risk of subsequent myocardial infarction (Luukinen et al. 2004). In a systematic review and met-analysis published in 2014, nine of twenty eight prospective studies included were found to demonstrate an association between OH and coronary artery disease, heart failure and arrhythmia and increased mortality, hazard ratio 1.36 (Angelousi et al. 2014). A recent prospective study in Italy has questioned the role of OH in predicting cardiovascular events (Casiglia et al. 2014). This study followed 1016 subjects over 65 years for over 12 years found that OH was not predictive of cardiovascular events when adjusted for age, sex and SBP.

Older people with OH and hypertension may have an elevated risk of developing cerebrovascular disease (Kario et al. 2002). It has been proposed that cerebral hypoperfusion may contribute to the development of small vessel white matter disease (Ryan et al. 2013). A cross-sectional study demonstrated that hypertensive patients with greater postural BP changes also have increased risk of advanced silent brain lesions and cardiovascular burden (Eguchi et al. 2004). In post-stroke patients, the appearances of OH symptoms has been linked with decreased cerebral blood velocity in the affected brain side which may be related to a stroke-induced impairment of CA (Matsui et al. 2005; Atkins et al. 2010). OH has been identified in about one quarter of patients attending an outpatient stroke clinic (Phipps et al. 2012), while in another retrospective analysis of 3222 patients with prior transient ischaemic attack, the prevalence of OH was reported to be 20% (Kwok et al. 2014).

2.8.4. Cognition

Beyond vascular risk factors, reduced cerebral blood flow may lead to cognitive dysfunction (Mills et al. 2007) and may to some extent explain the U-shaped association with SBP and cognitive function in older people (Glynn et al. 1999). According to the literature, three hypotheses can be formulated regarding the relationship between OH and cognitive impairment (CI).
“In neurodegenerative disease, OH and CI may result from a common pathological process which affects areas involved in both cognition and cardiovascular autonomic control. Alternatively, OH may lead to cerebral hypoperfusion which is supposed to play a role in the development of CI. Finally, recent data suggest that CI should probably be considered more a transient symptom of OH than a chronic effect”.

(Sambati et al. 2014)

The association of OH and long-term cognitive decline in the literature remains controversial to date and is limited by relatively small study sample sizes (Elmstahl and Rosén 1997), or others with comorbidities such as Parkinson’s disease (Allcock et al. 2006). In two longitudinal studies, OH was found not to be associated with CI (Viramo et al. 1999; Yap et al. 2008). The ARIC study showed that although OH was associated with less favourable cognition, the association was largely attributable to demographic and cardiovascular risk factors (Rose et al. 2010).

2.8.5. Falls

Falls are a leading cause of disability and economic consumption in the older population (Freedman et al. 2006). OH was found to be an independent risk factor for falls in a prospective study of 544 nursing home residents (Ooi et al. 2000), however the causal relationship between OH and falls has been difficult to quantify consistently due to confounding factors in this complex, heterogenous population. Although theoretical mechanisms linking OH and falls exist, a recent review of the subject has highlighted the methodological inconsistencies and lack of standardisation of orthostatic assessments and analysis in the literature to date, making it difficult to draw firm conclusions regarding the association between falls and OH (Shaw and Claydon 2014).

2.8.6. Frailty

Frailty can be defined as a clinical syndrome which encompasses “any three of the following criteria, unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity” (Fried et al. 2001). There is emerging literature that OH may be a physical marker of frailty and represent “a final common pathway of various forms of disordered physiology”
(Wieling and Schatz 2009). Recent studies have highlighted the potential associations of impaired HR response and BP recovery patterns and frailty (Romero-Ortuno, Cogan, O’Shea, et al. 2011). A population based study of 1347 older people concluded that OH may be a marker of the system dysregulation seen in frailty, although when adjusted for frailty, OH was not a significantly associated (Rockwood et al. 2012).

2.9. Principles of Managing OH

A wide range of both pharmacological and non-pharmacological therapeutic measures can be used in the treatment of OH. In the first instance, each patient should have a thorough medication review with consideration to discontinuation of medications known to have vasoactive properties. Adequate hydration is essential to avoid precipitous BP drops due to the haemodynamic effects hypovolaemia. Treatment should be directed towards improvement of symptoms and patient’s functional status and in reducing the risk of falls and syncope, rather than in achieving arbitrary BP goals. Options for further treatment include non-pharmacological and pharmacological measures which will be discussed. Non-pharmacological treatment strategies should be the initial approach to managing OH in an older person, followed by consideration of pharmacological measures if necessary.

2.10. Non-pharmacological Management

2.10.1. Elastic Compression Therapy

Elastic compression stockings (ECS) are frequently recommended for those affected by recurrent OI (Maggi and Brignole 2007). Their potential therapeutic benefit is based on the principle that external counter-pressure of the lower limbs or abdomen will reduce venous pooling and capillary filtration following orthostasis (Downie et al. 2008; Avril et al. 2010). Several studies have demonstrated short-term improvements in orthostatic BP by applying counter-pressure to the whole leg or lower abdomen (Denq et al. 1997; Smit et al. 2004; Podoleanu et al. 2006; Platto et
al. 2009; Stenger et al. 2010). Two recent systematic reviews have reported on the benefit of abdominal or full length compression in comparison to below knee or thigh length compression (Mills et al. 2014; Smeenk et al. 2014), however the authors of both reviews highlighted the paucity of high quality evidence regarding efficacy due to small sample sizes and variable study design incorporating different orthostatic stressors, which included lower body negative pressure, head-up tilting (HUT) and anti-gravity suits.

Another study has questioned the role of ECS for managing OH (Protheroe et al. 2011). This was a randomised, double blind, placebo-controlled study of fifteen healthy subjects using lower body negative pressure and head-up tilting as orthostatic stressors. ECS had no effect on orthostatic BP decline, and the authors highlighted the need for individualisation of therapy including consideration of anthropometric variable such as calf size which may influence the compressive effect of ECS. It has been shown that ECS exerting higher pressure on the calf than on the ankle show greater efficacy in increasing the venous ejection fraction from the leg (Mosti and Partsch 2011), and that in future trials, pressure and stiffness measurements of compression should be declared.

2.10.2. Physical Counter-manoeuvres

Physical manoeuvres used to treat OH are thought to increase venous return by activation of the lower limb skeletal muscle pump, reducing peripheral capacitance and increasing TPR. Those that increase muscle skeletal tone, including leg crossing and muscle tensing in younger patients with ANF, who suffer from severe OH, can promote venous return and raise CO (Ten Harkel et al. 1994; Bouvette et al. 1996; Smit et al. 1999; Van Lieshout et al. 2003). These physical measures can also be used in patients with vasovagal syncope to counteract their OI (van Lieshout et al. 2001; Krediet et al. 2005). Leg crossing and muscle tensing has been shown to increase MAP and may postpone or prevent syncope (Wieling et al. 2004; Krediet et al. 2005; van Dijk et al. 2005). Although these manoeuvres may result in favourable haemodynamic changes in younger patients with ANF, their practicality in an older, more complex patient group has not been assessed to date.
2.10.3. Sleeping in the Head-Up Position

Sleeping in the head-up position (SHU) has been used by clinicians for treatment of OI for over seventy years (Wieling et al. 2009). SHU has formed part of the management plan for orthostatic OH in patients with severe ANF (van Lieshout et al. 2000; Brignole, Alboni, Benditt, Bergfeldt, Blanc, Bloch Thomsen, et al. 2004; Cooper and Hainsworth 2008), POTS and more recently in patients with postural-related syncope (Cooper and Hainsworth 2008). SHU is thought to lead to a reduction in nocturnal polyuria, resulting in a decrease in renal arterial pressure, with subsequent activation of the RAAS and the release of vasopressin contributing to an increase in systemic BP (Bannister et al. 1977). The literature regarding efficacy of SHU is limited to studies including small numbers (less than twelve), younger patients with PAF, which may not be generalizable to an older, more heterogeneous population with OH (Ten Harkel et al. 1992; Wieling et al. 2009).

SHU is used frequently by physicians treating OH (Fan et al. 2006), with two-thirds of clinicians recommending angles less than 10°, with the most common angle of 5° elevation. Fan et al. have also recently demonstrated in a trial of one hundred patients with OH using SHU at six inches, that SHU had no significant haemodynamic effect on orthostatic BP. This is the largest study to date investigating the efficacy of SHU and questions its’ role as a therapeutic measure in OH (Fan et al. 2011).

2.10.4. Fluid Bolus Treatment

Ingestion of 475 ml of tap water within three to four minutes of standing can lead to a rise in BP in patients with OI (Jordan et al. 1999; Shannon et al. 2002). The systemic effect on BP is evident after five to ten minutes and is thought to be as a result of sympathetic reflex leading to vasoconstriction induced by the hypotonicity of the water rather than a volume effect (Jordan et al. 2000). Another study evaluated the effect of water versus clear soup in patients with MSA and POTS (Z’Graggen et al. 2010), with lower BP reductions demonstrated with water bolus treatment in the MSA group indicating the potential postprandial effect of soup ingestion in patients with autonomic dysfunction.
2.10.5. Salt Supplementation

Sodium may be supplemented by adding extra salt to food or taking 0.5-1g salt tablets to counteract symptoms of OI (Low and Singer 2008). Another study demonstrated an improvement orthostatic BP responses in nine patients with OH following water and salt water ingestion (Raj et al. 2006). Patients using sodium supplementation should be monitored for weight gain, oedema and subsequent hypertension which can complicate management.

2.11. Pharmacological Treatment

2.11.1. Introduction

Pharmacological therapy of OH involves two main strategies. The first is the use of short-acting pressor agents to increase the BP for several hours per dose during the day, potentially avoiding nocturnal hypertension and associated complications. The second approach is the use of pharmacological agents to increase the blood volume, see Figure 2-5. This strategy is generally long-acting and will usually increase the BP during both the day and night, which may contribute to nocturnal hypertension. Several systematic reviews published recently have questioned the use of pharmacological agents in managing symptomatic OH, highlighting limitations in the quality of study design and heterogeneity of the population included (Logan and Witham 2012; Ong et al. 2013).
Figure 2-6: Management strategies in OH. Strategy A may result in consistently raised BP. An alternative strategy is to use short-acting pressor agents, which will result in transient increases in BP (Raj and Coffin 2013)
2.11.2. Short Acting Pressor Agents

2.11.2.1. Midodrine

Midodrine is a pro-drug with an active metabolite desglymidodrine whose active metabolite is a peripheral alpha-1 adrenergic receptor agonist and was approved by the FDA for the treatment of OH in 1996. It is known to cause venoconstriction and arteriolar constriction, thereby increasing CO and TPR. Two double-blinded parallel group trials of one hundred and seventy one and ninety seven patients respectively, compared midodrine (doses from 2.5 mg to 10 mg taken 3 times daily) with placebo over three to four weeks in people with symptomatic neurogenic postural hypotension (Jankovic et al. 1993; Low et al. 1997). Both trials found that a 10 mg dose of midodrine increased standing BP significantly more than placebo, one hour after the dose was taken. Supine BP also significantly increased with midodrine, but to a lesser extent than standing BP. Both trials showed some improvement in patient and investigator global assessment symptom scales with 10 mg midodrine three times daily.

Midodrine does not cross the blood-brain barrier and has a pressor effect due to both arterial and venous constriction. Patient sensitivity can be unpredictable requiring careful dose titration. Potential adverse effects include pilomotor reactions, pruritus, supine hypertension, gastrointestinal complaints, and urinary retention (Parsaik et al. 2013). Some patients symptoms worsen on midodrine, maybe due to adrenoceptor desensitization (Kaufmann et al. 1988). The treatment duration of midodrine tolerated by patients is generally short with a median of 259 days demonstrated in a study of 664 patients with OH (Shibao, Grijalva, et al. 2013).

A systematic review of the use of midodrine including eleven trials of 593 patients with OH demonstrated moderate confidence of improvements in prevention of syncope, very low confidence in improving symptoms and quality of life (Izcovich et al. 2014), with pilomotor reactions the most common side effect reported. Another systematic review and meta-analysis of seven trials including 325 patients demonstrated a significant increase in SBP and patient global assessment symptom scales with midodrine, however, concluded that there is low quality evidence to
support the use of midodrine for OH due to study imprecision, heterogeneity and increased risk of bias (Parsaik et al. 2013).

2.11.2.2. Dihydroxyphenylserine (Droxidopa)

Dihydroxyphenylserine and L-dihydroxyphenylserine (DL & L-DOPS) are synthetic amino acid noradrenaline precursors. L-threo-DOPS is the only pharmacologically active stereoisomer of dihydroxyphenylserine. It is decarboxylated peripherally to noradrenaline which is a vasoconstrictor. L-threo-DOPS is commercially available as droxidopa and was approved by the FDA for the treatment of neurogenic OH in 2014.

An early study of twenty patients with familial amyloid neuropathy who were administered droxidopa resulted in significant increases in plasma noradrenaline, supine BP and improvements in symptoms of OI with minimal side effects (Carvalho et al. 1997). In an open label, dose-ranging study of twenty six MSA and six PAF patients, 300 mg twice daily resulted in lower systolic BP reductions and an improvement in symptoms following orthostasis (Mathias et al. 2001). Administration of 200 mg and 400 mg droxidopa daily was demonstrated to improve symptoms of OI in one hundred and forty nine haemodialysis patients (Akizawa et al. 2002). In short term (4 weeks n=86) and long term studies (24-52 weeks, n=74), 400 mg droxidopa after dialysis was shown to attenuate BP reductions and result in an improvement in inter-dialytic symptoms (Iida et al. n.d.). Droxidopa was effective in attenuating BP reductions in ten patients with OH with central and peripheral ANS disorders (Freeman et al. 1999). In nineteen patients with severe OH, droxidopa improved BP and orthostatic tolerance (Kaufmann et al. 2003). More recently, an open label dose optimization study of the effect of droxidopa (100-600 mg) of one hundred and sixty two patients with neurogenic OH found significant improvements in symptoms, symptom impact on daily activities, an associated increase in standing SBP, and was well tolerated (Kaufmann et al. 2014).
2.11.2.3. Yohimbine

Yohimbine, is an alpha-2 antagonist which allows for an increase in sympathetic nervous system activity and increased noradrenaline release from sympathetic neurons (Biaggioni, Robertson and Robertson 1994). Yohimbine has been shown to result in similar pressor responses to midodrine in patients with OH (Jordan et al. 1998). In a single-blind randomised crossover treatment trial in thirty one patients with severe autonomic failure, a single dose of yohimbine (5.4 mg) was associated with an average 11 mm Hg improvement in standing DBP compared with placebo-treated patients (Shibao et al. 2010), with an improvement in reposted symptoms of OI.

2.11.2.4. Pyridostigmine

Pyridostigmine is a peripheral acetylcholinesterase inhibitor that is commonly used in the treatment of myasthenia gravis. This acts to increase acetylcholine concentrations in the autonomic ganglia. As the preganglionic sympathetic neuron is cholinergic, it is proposed to act as a facilitator for sympathetic preganglionic neurotransmission and is more effective when upright, potentially resulting in less supine hypertension (Singer et al. 2003). A randomised controlled trial of fifty eight patients with neurogenic OH demonstrated a significant improvement in postural BP decay without a significant increase in supine BP in the pyridostigmine group (Singer et al. 2006). A single blind, randomised, placebo-controlled, crossover study compared yohimbine and pyridostigmine and found significant improvements in DBP in the yohimbine group with no improvement in haemodynamic responses in those treated with 60 mg pyridostigmine (Shibao et al. 2010). Cholinergic adverse events of pyridostigmine include excessive sweating, diarrhoea and siallorhea which may limit its use in an elderly population specifically in those with Parkinson’s Disease.

2.11.2.4. Ephedrine and Pseudoephedrine

Ephedrine and pseudoephedrine are both sympathomimetic agents and act as direct and indirect (by the release of noradrenaline from the presynaptic neuron), α-1 adrenoceptor agonists resulting in vasoconstriction. Both have demonstrated
favourable haemodynamic effects pressor effects in patients with severe OH due to MSA or PAF (Fouad-Tarazi et al. 1995; Jordan et al. 1998). Unlike midodrine, they do cross the blood-brain barrier resulting in unfavorable side effects, although are currently rarely used in clinical practice.

2.11.2.5. Octreotide
Octreotide is a somatostatin analogue which inhibits release of gastrointestinal peptides, some of which have vasodilatatory properties, resulting in a net pressor effect (Hoeldtke and Israel 1989). The starting dose is usually between 25-50μg and is administered subcutaneously. In a study of eighteen patients with PAF, octreotide reduced postural, postprandial, and exertion-induced hypotension without causing or increasing nocturnal hypertension (Alam et al. 1995). Octreotide increased supine BP after acute and chronic administration in two studies patients with MSA (Bordet et al. 1994, 1995). In the latter study, which was an open label design including five patients with MSA, there was reported improvement in functional measures at six months with mean treatment duration of twelve months. In another study, the combination of midodrine and octreotide 1μ/kg was more effective in reducing OH than either drug alone (Hoeldtke et al. 1998).

2.11.3. Volume Expansion

2.11.3.1. Fludrocortisone
Fludrocortisone acetate is a synthetic mineralocorticoid with minimal glucocorticoid effects, leading to renal sodium reabsorption and an expansion in plasma volume. Following ingestion, fludrocortisone is readily absorbed and peak plasma levels are reached within 45 min with half-life reported to be around seven hours. Several early studies have demonstrated an increase in BP and improvement of symptoms when used for OH (Campbell et al. 1975; Hoehn 1975; van Lieshout et al. 2000), however these small studies included only six to eight subjects. Fludrocortisone should be used in caution in those with fluid overload or cardiac failure as increased fluid volume may precipitate pump failure (Freeman 2008). Supine hypertension resulting from the increase in peripheral vascular resistance and blood volume may complicate treatment with fludrocortisone. Other side effects include hypokalemia and ankle
oedema, with a study demonstrating that one in three will discontinue treatment within 6 months due to these adverse effects (Hussain et al. 1996). In another study, the median duration of fludrocortisone therapy in a retrospective cohort of 1103 patients was 254 days (Shibao, Grijalva, et al. 2013).

2.11.3.2. Erythropoietin
Anaemia can be frequently encountered in patients with ANF (Rao and Stamler 2002). Treatment of anaemia can help with blood volume depletion and treatment of exertional symptoms. In an open label study of eighty four patients with PAF, erythropoietin (EPO) three times weekly subcutaneously was demonstrated to improve standing BP, symptoms and mean haemoglobin (Biaggioni, Robertson, Krantz, et al. 1994). The use of EPO in a large study of patients with CKD with target Hb of 13.5g/dl found that EPO was associated with increased cardiovascular risk without an improvement in quality of life (Singh et al. 2006).
Chapter 3
Neuro-Muscular Electrical Stimulation
Literature Review
3.1. Motor Unit Anatomy

The motor unit can be referred to as the "final common path," as it is through motor units that all motor commands must be passed to produce movement (Sherrington 1910). A motor unit is composed of a motor neuron, its axon, and the muscle fibres the motor neuron innervates (Burke and Tsairis 1973). A single motor neuron and its associated muscle fibres can be considered the smallest unit of force that can be activated to produce movement. The average number of fibres innervated by a motor neuron is around 300, but may be as high as several thousand (Enoka and Fuglevand 2001). Muscles that act on larger body masses are composed of higher numbers of motor units in comparison to smaller muscles. Efficient contraction of individual and complex groups of muscles is possible due to the coordination of electrophysiological, metabolic, mechanical, and anatomical properties of the motor neuron and its muscle unit.

The waveform of contractile force during incomplete tetanus and the resistance of the muscle unit to fatigue can be used as criteria to classify motor units. An early classification system of motor units separated them into slow (S), fast fatigable (FF) and fatigue-resistant (FR) units (Burke et al 1967). A fourth motor unit type (FI), with a fast twitch and an intermediate fatigue resistance was later identified histologically (McDonagh et al. 1980). These basic motor unit types could be shown to be uniquely identifiable according to the metabolic pathways they used to produce force. From a more recent classification system, it is possible to differentiate the fibres into Type 1 (slow twitch) and Types 11a and 11b (fast twitch) fibres when stained by ATPase histochemical staining (Williamson et al. 2000).

In most skeletal muscle, slow motor units innervate “red” muscle fibres which are plentiful in mitochondria and myoglobin content and have a higher threshold to develop fatigue. Slow motor units are particularly important for activities that require sustained muscle contraction such as maintaining the upright posture. Fast fatigable motor units are specifically important for brief exertions that require larger force such as sprinting or jumping. Fatigue resistant motor units typically generate around twice the force of a slow motor unit and compromise muscles associated with longer
periods of continuous contraction such as paraspinal and soleus muscle activation while standing.

3.2. Neuromuscular Transmission

The basic function of a motor unit is to transform synaptic input received by the motor neuron into mechanical output by the muscle (Heckman and Enoka 2012). Each myelinated motor axon that reaches its target muscle divides into up to one hundred unmyelinated terminal fibres. The neurotransmitter acetylcholine (ACh) is synthesised in the terminal fibre close to the endplate and is stored in synaptic vesicles (SVs). Following the arrival of an action potential (AP) at the distal motor nerve ending, there is an abrupt opening of voltage gated calcium channels with a subsequent increase in intracellular calcium concentration (Cohen-Cory 2002). As a result of a complex of intracellular signalling events, SVs migrate to the surface of the nerve, and subsequently rupture and discharge ACh into the synaptic cleft. Nicotinic acetylcholine receptors located near the endplate of the muscle are activated by the released ACh, resulting in the influx of sodium ions into the muscle which depolarises the muscle leading to endplate AP formation. This AP is subsequently transmitted along the muscle membrane by progressive opening of sodium channels which eventually leads to a muscle contraction (Martyn et al. 2009).

3.3. Normal Voluntary Muscle Recruitment Patterns

The progressive recruitment of small, slower, motor units followed in order of increasing size to the larger, fast motor units is known as the size principle (Henneman et al. 1965). According to Ohm’s law $V = IR$, where $V$ is the voltage, $I$ the electric current and $R$ the resistance, the change in membrane potential in response to a synaptic current is proportional to the input resistance of the motor neuron. Smaller motor neurons tend to have higher input resistance, and are generally the first to be recruited in response to an AP, see Figure 3-1.
Figure 3-1: Graphical representation of orderly recruitment of motor units during voluntary activation of skeletal muscle
3.4. Electrical Stimulation

The first observation of motion following application of electrical wires to leg muscles severed from the body of frogs was reported in 1790, while in 1831, Faraday demonstrated that the application of electrical currents could stimulate nerves to create active movement (Cambridge 1977). Early studies investigated the effects of electrical stimulation for the enhancement of muscle function that can be used for “functional” purposes, facilitating muscle contraction in limbs compromised by stroke or injury (Liberson et al. 1961; Moe and Post 1962; Valenti 1964).

Over the past fifty years, Electrical Stimulation (ES) has been developed for clinical use incorporating a variety of clinical applications with several definitions used in the literature depending on clinical use. ES is frequently used in the rehabilitative setting to improve muscle strength and range of motion in weak or spastic musculature, decrease muscle atrophy, promote tissue healing, and decrease pain (Doucet et al. 2012). Higher frequencies (20-50 Hz) are generally used in neuromuscular electrical stimulation (NMES) and this form of stimulation is delivered to the chosen muscle in static conditions at current intensities sufficient to evoke visible muscle contractions (Doucet et al. 2012). Functional electrical stimulation (FES) refers to “the process of pairing the stimulation simultaneously or intermittently with a functional task in persons unable to actively perform these movements” (Thrasher and Popovic 2008). Transcutaneous electrical nerve stimulation (TENS) is primarily used for pain relief in a number of chronic conditions, with lower frequencies (<10 Hz) delivered at motor intensity or higher frequencies (> 50 Hz)) at sensory intensity (DeSantana et al. 2008).

3.5. NMES System Components

NMES is clinically available in two principle formats: transcutaneous (surface) and implanted (percutaneous, epimysial, epineural, intraneural, and cuff) (Grahn et al. 2014). These systems can either be constant-voltage or constant-current regulated, with the former more common in clinical practice, as this minimises the risk of high current densities at the tissue-interface electrode, and subsequently skin damage.
Broderick et al. 2008). In the clinical setting, surface NMES devices must be sufficiently easy to operate, with a navigable interface so that patients with physical or sensory limitations can use the equipment unaided or with minimal assistance. Most surface NMES systems follow a standard electronic design structure as previously described (Ilic et al. 1994), consisting of a digitally controlled stimulator with user interface, sensor interface, and power supply blocks, see Figure 3-2. Of principle importance are the NMES stimulus parameters, in particular pulse repetition rate (frequency), stimulus amplitude (stimulation intensity) and pulse duration, as they greatly influence the strength of the induced muscle contraction (Broderick et al. 2008).

Percutaneous NMES incorporates intramuscular needle electrodes that pass through the skin and stimulate target muscles (Caldwell and Reswick 1975; Stanic et al. 1978). Stimulation of deep muscles provides isolated, selective and repeatable muscle contractions. This system reduces the risk of local tissue injury although can contribute to other complications including the risk of displacement, electrode-related infection and granuloma formation secondary to retained electrode fragments (Knutson et al. 2002). This study of 858 implanted electrodes found the probability of an electrode remaining intact in the body at one year is 91%, with 16% of subjects subcutaneous developing granuloma formation.
Figure 3-2: Typical set-up of a trans-cutaneous electrical stimulator out-block (Broderick et al. 2008)
3.6. Frequency

Stimulation frequency refers to the number of pulses produced per second and is stated in units of Hertz (Hz, e.g., 30 Hz = 30 pulses per second). Most NMES clinical regimens use stimulation frequencies of between 20-50 Hz patterns for optimal results, although this can vary depending on the goals of intervention (Baker et al. 1988; de Kroon et al. 2005). At low stimulation frequencies, muscle fibres produce a series of muscle twitches, whereas at higher stimulation frequencies, these twitches fuse into a smooth contraction. The threshold frequency for eliciting a smooth muscle contraction is also referred to as the fusion frequency and the cumulative effect of repetitive stimulation is known as temporal summation (Peckham and Knutson 2005). For prolonged use, constant low frequency stimulation is typically used, which produces a smooth contraction at low force to facilitate reducing fatigue or discomfort (Bhadra and Peckham 1997).

3.7. Ramping of Stimulation Frequency

The period of time from when the stimulation is turned on until the actual onset of the desired frequency and intensity is termed the “ramp time” (Baker et al. 2000). This is specifically useful when treating conditions associated with increased muscle tone that creates resistance against the stimulated movement such as in those with limb spasticity following stroke. In this setting ramp times of 1 to 3 seconds are most commonly used, however longer ramp times can be used and individualised for patients with an increased sensitivity to stimulation (Bhadra and Peckham 1997). Ramp times also can be modified when stimulating specific multiple muscle groups such as standing and walking in patients with SCI to produce smoother gradations of tetany between individual muscles which more closely replicate natural movement (Bijak et al. 2005).
3.8. Stimulation Amplitude/Intensity

The term “stimulus threshold” defines the lowest level of electrical charge that generates an AP, which is identical to an AP formed naturally (Sheffler and Chae 2007). The intensity or amplitude is usually recorded in milliamperes (mA). Higher stimulation intensities induce stronger depolarising effects in the structures underlying the electrodes (Mesin et al. 2010), and are associated with increases in muscle strength following training programmes with NMES (Maffiuletti et al. 2002; Piva et al. 2007; Stevens-Lapsley et al. 2012). The effect of stimulation intensity on muscle fatigue has not been clearly defined (Doucet et al. 2012), and it has been suggested that stimulation frequency a more important variable (Gorgey et al. 2009), by possibly reducing the evoked torque relative to the activated muscle area.

3.8. Pulse width and duration

The pulse width or pulse duration is defined as the total time span of a single pulse. The output pulse waveform is normally monophasic, asymmetric biphasic or symmetric biphasic, see Figure 3-3. These shapes characterise electrical current whether it rises only (monophasic-direct current), or in addition, falls below (biphasic-alternating current) a zero baseline (Gracanin and Trnkoczy 1975). In biphasic pulses, the pulse duration considers both phases (McLoda and Carmack 2000). Asymmetric biphasic pulse trains are bidirectional and allow ions to flow in both directions minimising ion redistribution and subsequent risk of skin irritation (Broderick et al. 2008). Symmetric biphasic waveforms are associated with lower peak voltages necessary to reach sensory and motor threshold than monophasic stimulation (Kantor et al. 1994). Dynamic quadriceps extensions similar to those used in FES cycling tests exhibit pulse widths between 300 µs-600 µs (Janssen et al. 2004).
Figure 3-3: Common stimulus output trains: (a) Monophasic (b) Asymmetric biphasic (c) Symmetric biphasic (d) Symmetric biphasic with interpulse interval (Broderick et al. 2008)
3.9. Duty Cycle

The specific on and off time of an NMES program is referred as the duty cycle and is usually stated in ratio form, such as 1:3 (10 seconds on, 30 seconds off). The potential benefit of the duty cycle is that periods of rest have been shown to enable muscle tissue to recover more quickly and produce greater force when compared to constant stimulation patterns (Boom et al. 1993). Intermittent stimulation is commonly used in clinical practice to preserve force development and result in greater patient tolerance. The duty cycle can be modified to patient needs as well as the goals of therapy.

3.10. Duration of Stimulation Protocols

Duration of NMES protocols are highly variable and ultimately depend on the specific clinical application and muscles stimulated. A systematic review of nineteen trials investigating the use of FES for upper limb motor recovery following stroke found an array of protocols durations used (de Kroon et al. 2005). Protocol duration ranged from thirty minutes one time per day to one hour three times per day. Overall period of treatment varied from two weeks to three months, with increased benefits seen with shorter programs (2.5 hours/week) in comparison to those with longer programs (21 hours/week).

3.11. NMES Muscle Recruitment Patterns

The recruitment pattern of motor units through peripheral pathways using NMES does not follow size principle as outlined by Henneman (Trimble and Enoka 1991; Gregory and Bickel 2005). In contrast to this, ES imposes “a reversal of the motor unit activation order since large-diameter axons of the fast units are more easily excited by imposed electric fields than are small-diameter axons of the slow units” (Bickel et al. 2011). In addition to this, motor unit recruitment imposed by ES is termed superficial, spatially fixed, and incomplete (Gregory and Bickel 2005). The spatially fixed pattern of motor recruitment pattern refers to the principle of the same
motor units being repeatedly activated by pulses of electrical current which may result in muscle fatigue (Gondin, Cozzone, et al. 2011).

3.12. Muscular and Neural Adaptations to NMES

A study by Gondin et al. evaluated the chronic effects on muscle NMES over an eight week period in healthy individuals (Gondin, Brocca, et al. 2011). Increases in maximal voluntary contraction (MVC) (+30%) and neural activation (+10%) were significantly increased in the NMES group with hypertrophy of both Type 1 and Type 2 fibres. A fast-to-slow phenotype shift was demonstrated with strengthening of the muscle cytoskeleton. Another study including in vivo and in vitro analysis of the non-dominant quadriceps of a healthy individual following ES, found an increase in MCV of 12% with increases in myosin heavy chain content, and significant changes at the single muscle fibre level induced by electrostimulation resistance, preferentially affecting slower Type 1 fibres (Maffiuletti et al. 2006). Increases in the microcirculation of the musculature may also mediate the beneficial effects of surface NMES (Gerovasili et al. 2009; Angelopoulos et al. 2013).

Neural adaptations may occur with NMES strength training (Hortobágyi and Maffiuletti 2011). These include spinal and supra-spinal mechanisms, with somatosensory and nociceptive inputs associated with NMES use, leading to changes in motor cortical excitability, which can in turn contribute to functional improvements (Maffiuletti et al. 2002; Hortobágyi and Maffiuletti 2011). NMES may be able to modify the excitability of inter-hemispheric connections and possibly the balance between inter-hemispheric excitation and inhibition, leading to the hypothesis that “NMES training can be viewed as a neural rather than a muscular treatment technique, particularly for patients with neurological disease with intact lower motor neurons” (Hortobágyi and Maffiuletti 2011). Figure 3-4 summarises the conceptual framework of neural adaptation by NMES with comparison to the effects of normal voluntary strength training (VST).
Figure 3-4: Adaption during electrical stimulation training (EST) and voluntary strength training (VST). EST results in an increase in MCV by activation of ascending afferent input to the sensorimotor cortex (thick upward pointing black arrow). Induction currents are generated inside the muscle by EST (short downward pointing arrows). In contrast voluntary strength training has much smaller afferent input to sensory areas but large descending volleys that generate voluntary force and MCV (Hortobágyi and Maffiuletti 2011)
3.13. Limitations of Surface NMES

During clinical use, muscle fatigue due to NMES is usually the main limiting factor (Jubeau et al. 2008; Mackey et al. 2011) and may lead to muscle damage. More recently, a method to minimise muscle fatigue has been developed called spatially distributed sequential stimulation (Sayenko et al. 2014). This involves distributing the centre of electrical field over a wider area within a single stimulation site using an array of surface electrodes, alternating activation of sub-compartments. At a given stimulation intensity, the current passing through the tissue increases as the electrode size decreases, reducing patient tolerance due to higher current density adversely stimulating cutaneous sensory receptors. The use of larger electrodes is preferable as they result have been shown to result in less discomfort and greater subject tolerance (Alon et al. 1994; Petrofsky et al. 2008).

NMES-induced damage of the human medial gastrocnemius has been demonstrated to result in de-adhesive, disassembly, and disorganisation responses in the muscular contractile connective tissue (Mackey et al. 2011). During isometric conditions, NMES has been shown to be associated with a ten to thirty fold increase in creatinine kinase activity (Aldayel et al. 2010). A case of rhabdomyolysis was reported in a young male subject presenting with severe asthenia and increased levels of circulating muscle proteins induced by excessive NMES usage (Guarascio et al. 2004), and it has been suggested to use NMES with caution in patients who may be at higher risk of rhabdomyolysis such as those taking high dose statin therapy.

3.14. Clinical Applications of Surface NMES

Surface NMES has been widely used in the rehabilitative setting to enhance motor function for over fifty years. The application of NMES is limited to patients with intact lower motor neurons, excluding patients with polio, amyotrophic lateral sclerosis and peripheral nerve injuries (Peckham and Knutson 2005). Specific clinical applications in rehabilitation medicine include in patients post-stroke to enhance upper and lower limb motor recovery (Powell et al. 1999; Cauraugh et al. 2000; Kimberley and Carey 2002; Kottink et al. 2007), and those with oral and pharyngeal dysfunction (Bülow et al. 2008; Permsririvanich et al. 2009). NMES is
also effective in improving swallowing function in patients with dysphagia caused by non-stroke disease (Tan et al. 2013). Other neurological conditions that NMES has been used to facilitate motor function include cerebral palsy (Al-Abdulwahab and Al-Khatrawi 2009), reducing fatigue in multiple sclerosis (Chang et al. 2011; Coote et al. 2014), and stimulating low motor cortex excitability, measured by motor evoked potential, in patients with spinocerebellar ataxia (Chen et al. 2014).

NMES has been demonstrated to be an acceptable alternative to physical therapy in the management of patients with knee osteoarthritis and quadriceps femoris muscle weakness (Walls et al. 2010; Bruce-Brand et al. 2012), and improving quadriceps function and knee strength follow anterior cruciate ligament surgery (Taradaj et al. 2013). NMES has been shown to be efficacious in promoting physical recovery and exercise capacity in patients in the critical care setting (Vivodtzev et al. 2012; Ferreira et al. 2014), as well as preventing skeletal-muscle weakness in this group (Maffiuletti et al. 2013). In a small study, NMES was demonstrated to reduce quadriceps muscle deterioration in patients with severe exacerbations of chronic obstructive pulmonary disease (COPD), and may be used to complement post-exacerbation pulmonary rehabilitation (Giavedoni et al. 2012). A meta-analysis of eight trials involving 156 patients concluded that although NMES significantly improved reported dyspnoea, NMES did not lead to increased quadriceps muscle strength or an improvement in muscle fibre characteristics (Pan et al. 2014). Several studies have reported the benefits of NMES in increasing exercise capacity and skeletal muscle degradation in patients with chronic heart failure (CHF) (Nuhr et al. 2004; Dobsák et al. 2006), and increased adherence to cardiac rehabilitation programmes (Karavidas et al. 2010). A systematic review of eleven studies including 218 patients with COPD, CHF and thoracic cancer concluded that NMES is an effective means of improving muscle strength in those with progressive disease (Maddocks et al. 2013).

NMES has been developed as a therapeutic modality in patients with stress urinary incontinence, with improvements in eliciting strength of pelvic floor muscle contractions and a reduction in associated symptoms reported (Maher and Caulfield 2013). Another similar clinical application includes the use of NMES to enhance
anal sphincter tone and quality of life in patients with faecal incontinence (Ergun et al. 2010) and sacral nerve stimulation to treat older patients with constipation and associated faecal incontinence (Pinto and Sands 2009).

3.15. Haemodynamic Effects of Surface NMES

NMES has been recently advanced as a blood flow assist device (Breen et al. 2007, 2009). Calf muscle NMES has been shown to enhance lower limb venous blood flow in patients with chronic venous insufficiency (Clarke Moloney et al. 2006) and in healthy subjects (W Man et al. 2003; Morita et al. 2006; Broderick et al. 2010). In recent years, improvements in lower limb venous blood flow have been demonstrated in healthy subjects with calf muscle NMES resulting in duplex venous ultrasound peak systolic velocities of 13-120 cm/s in the popliteal vein (Davis et al. 1990; Raymond et al. 1999; Sampson et al. 2000; Faghri et al. 2001; Lyons et al. 2002; Chi et al. 2008; Corley et al. 2009; Griffin et al. 2010; Izumi et al. 2010). A study of the effect of footplate NMES in healthy volunteers demonstrated significantly higher femoral arterial blood flow recordings in addition to enhanced venous blood flow in the stimulated group (Varatharajan et al. 2014).

Another clinical application of NMES as a lower limb blood flow assist device include it’s potential in preventing venous stasis in healthy individuals (Izumi et al. 2010), and in those postoperatively to prevent venous thromboembolism (Broderick et al. 2013; Warwick et al. 2013). A recent systematic review of this application highlighted significant differences in terms of patient population, NMES delivery and diagnosis of venous thromboembolism and concluded that although NMES increases venous blood flow and is well tolerated, current evidence does not support it’s role in thromboprophylaxis (Hajibandeh et al. 2015).
3.16. Use of Surface NMES in Patients with OH Post Spinal Injury

Patients who have sustained spinal cord injury (SCI), exhibit low levels of efferent sympathetic nervous activity resulting in the loss of reflex vasoconstriction following orthostasis (Mathias 1995). Other contributing factors to developing OH in this group include altered baroreflex function, excessive pooling of blood in the abdominal viscera and lower extremities due to inactive skeletal muscle pump, cardiovascular deconditioning, and altered salt and water regulation (Claydon et al. 2006). The reduced blood volume in intra-thoracic blood vessels leads to a decrease in end-diastolic volume and resultant left ventricular SV and CO (Ten Harkel et al. 1994).

Raymond et al evaluated haemodynamic responses during lower body negative pressure in eight patients with paraplegia and the effect of ES induced leg muscle contractions in comparison to eight healthy controls (Raymond et al. 1999). ES decreased calf volume, increased SV (20%) and CO (16%), and decreased TPR (12%) during -30mmHg of negative pressure. Several studies have demonstrated NMES-induced contractions of the leg muscles increases CO and SV, effects that are attributable to increased venous return (Davis et al. 1990; Sampson et al. 2000; Chi et al. 2008). NMES of leg muscles was shown to increase CO and SV in six men with paraplegia, while performing arm-crank exercise at maximal effort (Faghri and Yount 2002). FES of the knee extensors and plantar flexors in two patients with tetraplegia and three patients with paraplegia resulted in higher SBP and DBP during graded tilt testing (Elokda et al. 2000). In another study of seven patients with tetraplegia and seven patients with paraplegia, lower limb NMES maintained SV, CO and TPR levels assessed by cardiac impedance technology at approximately baseline levels during 30 minutes of upright posture, with a greater effect seen in the group with tetraplegia (Faghri et al. 2001). The use of NMES has been reported to be beneficial in those with sub-acute phase SCI, leading to improvements in orthostatic tolerance during postural training, but retention and habituation of these effects are unknown (Hamzaid et al. 2014).

The quality of evidence available in the literature investigating the effects of NMES is limited to relatively few randomised controlled trials, non-randomised trials and
case series. In a systematic review of non-pharmacological interventions for OH post-SCI, Gillis et al. found that NMES of the legs resulted in an approximate 8/4 mmHg reduction in BP with NMES during an orthostatic challenge (Gillis et al. 2008). Another systematic review of FES post SCI included three Level 2 randomised controlled trials and six non-randomised trials and concluded that FES “may be an important treatment adjunct” to minimise cardiovascular changes during postural orthostatic stress in individuals with SCI (Krassioukov et al. 2009).

3.17. Clinical Applications of Implantable NMES

Percutaneous NMES has been found to be an effective treatment strategy in those with post-stroke hemiplegic shoulder pain, leading to improvements in quality of life (Renzenbrink and IJzerman 2004) and shown to be cost effective (Van Til et al. 2006). Another study investigated the effects of gluteal percutaneous NMES on long-term prevention of pressure ulcers in high risk patients and concluded that daily use is associated with improved indirect measures of tissue health and tolerance of sitting balance (Bogie et al. 2006). Implantable, intramuscular stimulation involves electrodes implanted directly into muscle while peripheral nerve stimulation relies on electrode cuffs that are surgically placed around nerves innervating target muscles (Grahn et al. 2014). This method of NMES is associated with higher rates of fatigability (Boom et al. 1993) and it’s current use is mostly confined to research environments (Peckham and Knutson 2005).

Direct stimulation of the spinal cord by epidural or intra-spinous stimulation (ISMS) may be advantageous over transcutaneous systems as this provides an opportunity to directly activate higher level circuitry which coordinates motor control (Minassian et al. 2004; Bamford and Mushahwar 2011). In epidural stimulation, electrodes are placed directly over the spinal cord (Hachmann et al. 2013). A recent report described a patient with chronic C7-T1 SCI and resultant paraplegia who received lumbar epidural stimulation and achieved the ability to full weight bear with assistance. The authors concluded that epidural stimulation might be responsible for the reactivation of previously silent spared neural circuits or promote plasticity (Harkema et al. 2011). Recent advances in the application of ISMS have shown...
promise in restoring locomotor function in patients with SCI, although it’s clinical use is currently confined to experimental studies (Etlin et al. 2014; Guertin 2014).
Chapter 4
Methodology
4.1. Study Design

The studies in chapters six to eight inclusive comprised a randomised crossover study design (Pocock 1984). Each subject underwent three successive 180 second HUT or active stand procedures in each protocol. To minimise the possibility of an order effect, each intervention was preceded by a period of five minutes resting supine to enable haemodynamic stabilisation. The interventions for each HUT included alternate leg calf muscle NMES, simultaneous leg calf muscle NMES and control for the studies in chapters six and seven. Alternate leg NMES was chosen as the stimulation setting in chapter eight with control and ECS interventions. The order of intervention was randomised by closed envelope technique as previously described (Torgerson and Roberts 1999).

4.2. Study population

The subjects recruited for the studies in chapters six and eight were identified from a database created by the Health Inequalities and Ageing in the Community Study (HIACe) (Humphreys E and deBurca S 2008). This study comprised a quantitative research strategy and cross-sectional research design conducted in the Limerick City area between 2007-8. This involved both a social study component and clinical evaluation of healthy, community dwelling older adults in the Thomand cluster on the north-side of Limerick city. The objectives of this study were to examine the association between socio-economic status and health status in an older population and to identify the main demographic and socio-economic characteristics of people associated with variations in health status. A secondary objective was to explore the relative importance of intervening factors such as the environment of neighbourhood, social capital, health services utilisation and quality of health care and health services delivery.

542 subjects completed the social study which involved the administration of the SF36 survey, which measure eight dimensions of self-assessed health (Ware and Sherbourne 1992). 392 subjects completed the clinical research component of the study that included health screening of respondents surveyed to establish objective
measures of health status. Detailed physiological assessments of each participant were completed including haematological profile, respiratory (pulmonary function), cardiovascular (head-up tilt, ambulatory BP, 24 hour holter monitoring and echocardiography) and bone health studies (bone densitometry). Head-up tilt (HUT) files from participating subjects were analysed and those who fulfilled the diagnostic criteria as per the 1996 consensus statement (Kaufmann 1996) for OH were identified and recruited.

4.3. Sample Size Calculation

Sample size determination for the studies in chapter six to eight inclusive were based on estimates of an alpha of 0.05, power of 0.8, with a repeated measures design (within subject comparisons between baseline and each condition). A previous study demonstrated that toe raising and marching on the spot can increase SBP by 20-23 mmHg (Bouvette et al. 1996). Similarly, another study found that with lower body muscle tensing, the minimum drop in mean arterial pressure (MAP) was 19mmHg higher in patients with IOH (Krediet et al. 2007). Based on these observations, a minimum of 7 subjects would be required to show an improvement of 20mmHg. To maximise ability to detect changes, and to account for subject dropout, recruitment of twenty subjects was targeted for the study in chapter eight.


The gold standard for BP measurement is the invasive placement of an intra-arterial catheter in a peripheral vessel including the radial, brachial or femoral artery. Intra-arterial catheters are currently used infrequently unless in the critical care setting as they can contribute to local infection, pseudo-aneurysm formation and arterial dissection (Moran et al. 1988). Over recent years, development of non-invasive methods of BP measurement has included incorporating a pressure cuff on the finger, using the volume clamp method as implemented in the Finapres (Ohmeda Monitoring Systems). During this period, non-invasive and relatively easy to use
devices have been developed and validated for the assessment of BP. The Finapres, and its successors, Portapres and Finometer (Finapres Medical Systems) have become the most frequently used method of continuous arterial BP measurement.

4.4.1. Finometer Equipment and Set-Up

The Finapres method of operation is based on the volume clamp method of Peñáz (Peñáz 1975). This is based on the development of dynamic (pulsatile) unloading of the finger arterial walls using an inflatable finger cuff with built-in photo-electric plethysmograph. TNO-Biomedical Instrumentation made considerable improvements to the Peñáz volume clamp method by developing the ‘Finapres’, which enabled the continuous measurement of finger arterial BP in clinical settings (Imholz et al. 1998). The device used for non-invasive BP recordings in the studies included in this thesis was the Finometer PRO, which also includes a height correction sensor and Modeflow technology to derive additional haemodynamic parameters such as stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR).

Figure 4-1 illustrates the Finometer set-up. An air bladder lines the inflatable cuff and contains an infrared emitter. The cuff is wrapped around the middle phalanx of the second or third fingers and the photo-plethysmograph measures digital artery diameter fluctuations in the finger. Using a connection to compressed air, the cuff is inflated until the pressure exerted by the cuff equals the intra-arterial pressure. At this point, the trans-mural pressure (the pressure difference across the arterial wall) equals zero and the arterial wall is said to be "unloaded". The photo-plethysmograph now measures the diameter of the artery and this unloaded diameter is maintained by continuous, automatic adjustments of cuff pressure. The cuff pressure is therefore constantly maintained at intra-arterial pressure.
Figure 4-1: Frontend of finometer device with height detection module and cuff electrode placed on the finger
Figure 4-2 shows a block diagram of the Finapres BP monitor. The inflatable cuff contains an infrared transducer and is wrapped around the middle phalanx of the middle or index finger, so that the photo plethysmograph measures blood volume fluctuations in the finger. The cuff is connected to a source of compressed air, and the air pressure in the cuff and in the plethysmogram is linked by an electropneumatic transducer and a fast reacting servo system (30Hz bandwidth).

Figure 4-2: Simplified block diagram of the Finapre blood pressure set-up (Dorlas et al. 1985)
4.4.3. Physiocal operation

Figure 4-3 demonstrates the pressure in the finger cuff is increased in standardised increments (trace 1). As the cuff pressure increases, pulsations in the plethysmogram (trace 2) increase to a maximum level, then decrease again. The cuff pressure at the time of greatest fluctuation in the plethysmogram (point ‘a’ in trace 2) is considered to be the best estimate of the pressure at which the cuff pressure is equal to the transmural pressure. At this pressure, several more plethysmograms are analysed, and the servo set-point (trace 3) is adjusted again at point b. Once the unloaded state has been established, the servo loop is then closed, and finger pressure is measured.

After the initial calibration, the physiocal procedure is then applied i.e. at regular intervals, BP recordings are interrupted, and the set-point is checked. As the set-point stabilises, the interval between physiocal calibrations increases until 70 beats have elapsed, or approximately 1 minute.
Figure 4-3: Finapres start-up and physiocal adjustments (Imholz et al. 1998)
4.4.4. Accuracy of Finapres

Since its introduction, many studies have been carried out to validate Finapres measures of BP with established reference techniques. A review of 43 studies to assess the accuracy of the Finapres (Imholz et al. 1998) concluded that Finapres accuracy and precision is reliable for tracking of beat-to-beat BP, although is not precise enough for measurement of absolute BP in comparison to previously defined standards (White et al. 1993). There are a number of reasons why Finapres BP measures would differ from established reference measures. The arterial pressure waveform in the finger is affected by both pressure wave reflection from the periphery, and the pressure gradient in the arterial system. Peripheral reflection causes an augmentation of the systolic peak pressure, and the arterial pressure gradient results in lower measured mean and diastolic pressure (Omboni et al. 1993).

4.4.5. Accuracy of Modeflow

A number of studies have been performed investigating the accuracy of Modeflow estimates of SV in comparison to gold standard methods. A study of ten healthy young participants during orthostatic stress comparing Modeflow derived SV and intra-brachial arterial BP thermodilution-determined SV showed no significant difference in measurements (Harms et al. 1999). Another study of forty physically active patients compared Modeflow SV with whole body impedance cardiography (Nieminen et al. 2000), and concluded that Modeflow is useful for tracking changes in SV, but is less reliable for measuring absolute values.

Modeflow SV measures were well matched the supine position when compared with doppler ultrasound flow velocity. SV measures were well matched the supine position, but that systemic differences appear during 30° HUT (van Lieshout et al. 2003), with Modeflow underestimating the drop in SV by 10.5%. Based on these studies, it is clear that the accuracy and reliability of Modeflow derived SV estimates remains in doubt and limitations exist for drawing firm clinical conclusions. For this reason, Modeflow data was included only in the feasibility study in chapter six to assess for any clear trends in SV response to NMES.
4.4.6. Finometer Trace in Identifying OH

Beatscope® software allows for the automated measurement of SBP, DBP and HR across several cardiac cycles. A minimum of three cardiac cycles is necessary to obtain mean systolic, diastolic and heart rate (HR) values. Baseline haemodynamic parameters are calculated by the statistical analysis application of the Beatscope® software package. A further analysis of the values at the lowest systolic blood pressure (SBP) and diastolic blood pressure (DBP) or nadir is calculated. The difference between baseline and nadir values is termed the “delta” which is used to diagnose OH as per consensus guidelines (Kaufmann 1996). There is some evidence that 5-second averaging of Finometer outputs are more predictive of falls (van der Velde et al. 2007) and this method was employed in trace analysis for the studies in chapter six to eight inclusive see Figure 4-4 and 4-5.
Figure 4-4: Beatscope® output demonstrating raw data pulse wave morphology from baseline to onset of tilt (event mark) and recovery
Figure 4-5: Beatscope® output incorporating 5 second averaging. Hatched areas included in statistical analysis (left-baseline SBP, DBP and HR, right-nadir SBP, DBP and HR)
Figure 4-6: Beatscope® statistical analysis output table with average values for haemodynamic parameters
4.5. Orthostatic stressor

Orthostatic challenges used to investigate neuro-cardiovascular instability may be passive, such as the HUT test or active challenges including the squat-stand test, sit-stand test or the supine-stand test (commonly called the active stand). There are significant physiological differences between these methods which are reflected in variations of haemodynamic parameters. During active challenge when assuming the upright posture, venous pooling and microvascular filtration is countered by the skeletal muscle pump as previously described. The main difference between active and passive challenges lies in the reduction of TPR observed in the seconds after active standing, which may result in larger, immediate blood pressure reductions as seen in those with initial orthostatic hypotension (IOH) (Wieling et al. 2007). A direct comparison of squat-stand testing and HUT testing demonstrated that the active challenge resulted in a greater initial reduction in BP drop, although similar reflex compensatory responses were demonstrated (Rickards and Newman 2003). Another comparative study of fifty one adolescents and children demonstrated increased cardiac sympathetic activation with active standing (Matsushima et al. 2004), and concluded that either orthostatic stressor is appropriate to evaluate disorders of orthostasis.

The use of a passive challenge such as HUT in the assessment of older people with mobility problems is potentially advantageous in comparison to an active challenge which may be more practically difficult. Finometer trace quality is better with passive orthostatic challenges as there can be significant artefact with the movement required to achieve the upright stance actively. These various advantages have led to the adoption of HUT as a stressor in both clinical and research studies in patients with symptoms of OI or unexplained syncope (Brignole, Alboni, Benditt, Bergfeldt, Blanc, Thomsen, et al. 2004).
4.6. Head-Up Tilt Protocol

Head-up tilt (HUT) testing has been used to investigate disorders of orthostasis for over seventy years (Hellebrandt 1943). The protocol for HUT, which may include pharmacological provocation has been developed over the past thirty years for the investigation of unexplained syncope in all age groups (Kenny et al. 2000). A three HUT protocol was included in studies described in chapters six to eight. As per ethical approval, subjects were asked not to discontinue any of their usual medications or modify their lifestyle prior to undertaking the study protocol. They were asked to fast for a maximum of two hours beforehand. Studies were performed in a quiet syncope laboratory room at a temperature of between 21-23°C, in the Saint Camillus’ Day Hospital, University Hospital Limerick. Each protocol was completed between 9am and 5pm. Subjects were required to rest in the supine position for five minutes prior to the onset of a 70 degree positive HUT. An appropriate sized cuff was applied to the index or middle finger as recommended by the manufacturer. Warming of the hand was occasionally necessary to improve signal pick up by using a pre-warmed heat pack encompassing the monitored hand. The hydrostatic height correction system was used to compensate for hand movements with respect to heart level and a height nulling procedure (with the zero mark at the level of the right atrium). The HUT was performed using a motorised (CNSystems) tilt table with foot-plate and was sustained for three minutes as per European Society of Cardiology guidelines (Brignole, Alboni, Benditt, Bergfeldt, Blanc, Thomsen, et al. 2004). Continuous cardiac monitoring was performed using three lead ECG.

4.7. Active stand protocol

In the study described in chapter eight, subjects underwent a supine to stand orthostatic test (active stand) with continuous, non-invasive beat to beat BP recording as described above. Subjects completed the change from supine to standing within three seconds, with assistance provided by research staff to facilitate this where necessary. After standing, the BP was monitored for three minutes with subjects standing motionless with the monitored arm resting extended across the chest, with influence from the hydrostatic height correction system as outlined. If the subject experienced severe symptoms or signs of impending syncope, the active
stand was abandoned and the subject assisted back to the supine posture as soon as possible.

4.8. NMES device

The NMES device used in the studies in chapter six to eight inclusive is a custom built, portable, two channel stimulator, developed in the Department of Bioelectronic Engineering, NUIG who collaborated with this research (Duo-STIM, Bioelectrics Research Cluster, NUI Galway) (Breen et al. 2009). This stimulation device comprises a control processor, voltage regulator connected to high voltage supply and a bridge of control switches. The processor acts as a dedicated stimulation controller so that specially designed stimulation profiles can be implemented and evaluated. The microcontroller typically generates two sets of control signals according to the selected algorithm, one to control the output pulse shape and a second to control the output stimulus amplitude. The device can store user parameters in memory and can be interfaced easily with external personal computers or controllers. The separate Duo-STIM's programmer unit is a battery powered device incorporating a touch screen interface which allows a clinician to select the algorithm to be executed by the stimulator and adjust the algorithm's parameters such as maximum stimulus intensity, stimulation pulse width and frequency. The user of the portable Duo-Stim device is only required to access a minimum control set including alteration of stimulation intensity and activation of a test pulse if necessary.
Figure 4-7: Duo-Stim programmable device and attached electrodes
4.9. NMES Protocol

To facilitate NMES, two 5 cm×5 cm PALS self-adhesive, hypo-allergenic, skin surface electrodes (Nidd Valley Medical Limited, England) were placed over the motor points of the soleus muscles of both legs. The Duo-Stim device was programmed to provide a pulse width of 350µs, an inter-pulse interval of 100µs, a frequency of 36 Hz, a contraction time of 1.2 s, a ramp up time of 500ms and ramp down time of 300ms (Broderick et al. 2010), see Figure 4-8. The studies presented in chapter six and seven, incorporate two simulation patterns: alternate leg calf muscle stimulation at 3 second intervals and simultaneous calf muscle stimulation at 3 second intervals.

During the initial set-up, a series of test pulses were applied initially at a very low intensity. This part of the protocol lasted several minutes and the stimulus intensity was gradually increased manually until a noticeable contraction was observed for both legs, as indicated by a visible tightening of the soleus muscle or slight plantar flexion. The stimulation intensity was increased further to the comfort tolerance of the subject. At this stage, decision on stimulus intensity to be used during the protocol was recorded. The NMES device was switched on at onset of HUT and was under manual control by a research assistant. The NMES device was switched off after three minutes at the onset of the tilt table returning to supine.
Figure 4-8: Electrode placement
Figure 4-9: Duo-Stim set-up and stimulation pattern (Broderick et al. 2010)
4.10.1 Duplex ultrasound

Duplex ultrasound incorporates B-mode real-time imaging and pulsed Doppler analysis of the velocity of flowing blood in arteries and veins. Vessel blood flow can be assessed using the variables of velocity of flowing blood, velocity of sound in tissue, the difference between frequency of transmitted and reflected sound, and the cosine of the angle of the ultrasound beam to the direction of flowing blood (Barber et al. 1974). Modern ultrasound units incorporate software that calculates these variables with this information displayed in typical output form seen in Figure 4-9.

4.10.2. Training in ultrasound technique

At the start of my research studies I attended the Wessex scientific vascular ultrasound course in Manchester, UK in September 2010. This is an internationally renowned annual training course specifically aimed at those new to ultrasound with emphasis on basic methodology and practical experience. In addition to didactic lectures on ultrasound methodology I received intense individual tuition from experts on popliteal venous ultrasound technique. In addition to this I regularly attended ultrasound sessions in the Saint Camillus’ Day Hospital, University Hospital Limerick, with a certified vascular ultrasound technician with supervision of reproducibility of popliteal vein peak systolic velocity and venous blood flow, however these recordings were not formally verified.

4.10.3 Duplex Scanning Protocol

Duplex ultrasound was used to monitor the subjects’ lower limb haemodynamic response during each intervention using a Siemens Sonoline Sienna® ultrasound machine with a broadband array probe (Frequency 5–13 MHz). An angle correction not exceeding $60^\circ$ was used and matched to the diameter of the popliteal vein. All measurements were performed by myself and were taken from popliteal vein of the right leg. Baseline blood flow measurements were recorded during the resting protocol with the subject supine. Three measurements were taken per parameter following assumption of the upright posture with the average of these used in the
final analysis (Clarke Moloney et al. 2006; Izumi et al. 2010). Peak venous velocity was recorded from the popliteal vein and the unit’s software was used to calculate volume flow (ml/min). Venous volume was calculated by multiplying the average blood flow velocity by the cross-sectional area of the popliteal vein.
Figure 4-10: Screenshot of duplex ultrasound software output showing peak systolic velocity and venous flow volumes
Figure 4-11: HUT set-up with ultrasound and Duo-Stim
4.11. Elastic Compression Stockings and Pressure Monitoring

Thigh length class 3 ECS (34-46 mmHg) were used in chapter eight (Medivan®). The ECS were applied by research staff with each subject lying supine during the five minute rest period between interventions with the assistance of a slip sheet. The ECS were subsequently removed following the three minute intervention while lying supine allowing the finometer traces to return to baseline during the subsequent five minute resting interval.

Sub-elastic compression pressure was measured with an electronic manometer (Kikuhime® TT Medi Trade, Soledet 15, DK 4180 Soro), see Figure 4-11 and 4-12. This device has been shown to accurate and precise in determining sub-compression pressure (Partsch 2005; Van den Kerckhove et al. 2007; Flaud et al. 2010). The small, flexible air filled pressure bladder has a dimension of 30 x 38 mm and is about 3 mm thick when calibrated to zero, see Figure 4-14. The sensor was applied 4-5 cm superior to the medial malleolus on the right leg for each subject, see Figure 4-15. This was applied prior to the ECS and secured in place with adhesive tape. Pressure was recorded in mmHg from the digital output screen following assumption of the upright posture.
Figure 4-12: Sub-bandage pressure monitor and sensor
Figure 4-13: Sub-bandage pressure monitor and sensor placement
4.12. NMES comfort evaluation procedure

In chapters seven and eight subject comfort of NMES was assessed during each protocol. As previously described, at each of the two time points (just after set-up of the NMES and at the end of each protocol), comfort was assessed by asking subjects to mark their level of comfort using a 100 mm, non-hatched visual-analogue scale (VAS) (Broderick et al. 2011). Mild pain was categorised as a VAS of 30 mm or less with moderate pain, between 31 and 69 mm, and scores of 70 mm or greater as severe pain. The minimum clinical significant difference (MCSD) in VAS was set as an increase in scores between test stages of 12mm (Kelly 2001).

At the conclusion of the study, each subject was asked to complete a short verbal questionnaire, which included a verbal categorical rating of the NMES treatment as very comfortable, comfortable, bearable or unbearable. Subjects were then asked if they would consider NMES an acceptable form of treatment. In chapter seven participants were asked regarding their preference of NMES stimulation pattern between asynchronous or synchronous stimulation patterns.

4.13. Orthostatic symptom evaluation

Following return to supine following each intervention, subjects were asked to describe any symptoms they experienced during the test. Individuals were only deemed symptomatic if they described one of the symptoms listed previously (Freeman 2008). Severity of symptoms of orthostatic intolerance were assessed by asking subjects to mark their level of discomfort using a 100 mm, non-hatched VAS at the end of each HUT or active stand. The research assistant facilitated completion of the VAS while supine, with the same grading scale as outlined above used (Kelly 2001).
4.14. Ethical Approval

Local Research Ethics Committee approval was obtained from University Hospital Limerick Research Ethics Committee. All participants gave written informed consent prior to the inclusion in the studies included in this thesis. The ethical approval confirmation letters are located in Appendix A.
Chapter 5
Therapeutic Use of Compression Stockings for Orthostatic Hypotension: An Assessment of Patient and Physician Perspectives and Practices

*Article published as short report Age and Ageing 2015*
*Abstract published Age and Ageing supplement 2014*
*Abstract published Irish Journal of Medical Science 2011*
5.1. Introduction

Non-pharmacological treatment measures form an important aspect of limiting BP reduction on standing. Avoidance of triggers and encouraging adequate hydration should be reinforced at the initial assessment. Specific measures aimed at expanding blood volume include water bolus treatment and sodium supplementation (El-Sayed and Hainsworth 1996). Other non-pharmacological therapeutic measures include SHU of the bed in an elevated position is thought to reduce nocturia (Fan et al. 2011), and physical counter-manoeuvres such as toe-raise, leg-crossing, thigh contraction, and bending at the waist have been shown to reduce venous capacity, increase total peripheral resistance and attenuate BP reductions (Bouvette et al. 1996).

Compression hosiery may be used for those affected by recurrent orthostatic intolerance and are frequently recommended. Up to 800 ml of blood can translocate into the lower limbs following several minutes in the upright posture (Brown and Hainsworth 1999). The rationale of using graduated compression garments is to apply external counter-pressure to the lower limbs or abdomen with the effect of reducing venous pooling and capillary filtration resulting in increased venous return (Privett et al. 2010). Garments applying counter-pressure to lower limbs have resulted in short term attenuations in BP reductions (Podoleanu et al. 2006), while those that compress the abdomen have shown greater promise in those with OH (Smit et al. 2004).

In clinical practice, older patients with OH who use ECS often report practical difficulties that may limit their potential benefit. To our knowledge, there has been no previous study that has evaluated these issues, or the prescribing practices of physicians that use ECS for OH. In view of the lack of information on this subject, two surveys were conducted. The first was a survey of patients with OH who were known to have been prescribed ECS. The aims of the patient survey were to assess compliance levels and explore reasons for non-compliance. A secondary objective was to record patient views on tolerability and effect of ECS on symptoms. A second
survey was undertaken of consultant physicians in geriatric medicine who would frequently be involved in managing older patients with OH. The aims of the physician survey were to assess their prescribing practices and views regarding the usage of ECS for this indication. A secondary objective was to measure the degree of consensus between physician and patient responses.
5.2. Methods

Questionnaire design and piloting was performed based on published guidance (Burns et al. 2008), and previous work investigating compliance levels of ECS post lower limb venous thrombosis (Kahn et al. 2003; Roche-Nagle et al. 2010). Using a panel of consultant physicians in geriatric medicine and senior nurse specialists we developed both questionnaires to assess key themes outlined above using single choice answer or Likert scale where possible. The patient questionnaire was tested for clarity on a random sample of ten older patients who attended the affiliated ambulatory day hospital service, with minor modifications undertaken based on patient feedback and experience. These data was not included in the final analysis.

5.2.1. Patient Study Group

The finalised survey was an anonymous postal questionnaire printed on coloured paper with return postage prepaid sent to ninety community dwelling patients with OH. In the case of each of these patients, a prescription for Class 2-3 thigh length ECS had been provided at discharge from hospital or in the outpatient clinic and these data were available from the patient record. Baseline characteristics including previous medical history, concomitant medication usage and type were recorded at the time of prescription of ECS. These patients were randomly selected from a computerised database maintained by staff in a regional syncope tertiary referral centre. Those with a history of significant cognitive impairment, previous DVT, chronic venous insufficiency and those who had subsequently died were excluded. The patient survey included items relating to compliance, reasons for non-usage and perceived effect on symptoms. Patient responses were identifiable to enable characterisation. To encourage responses, a reminder letter was posted three weeks later to those patients who did not return their questionnaire.
5.2.2. Physician Study Group

The second survey was administered electronically using an internet based survey package to sixty nine hospital based consultant physicians in Geriatric Medicine in active clinical practice in the Republic of Ireland. In this anonymous survey, participants were asked questions relating to their own current practice of ECS prescription for OH, which included items on preferred size, strength, estimates of patient compliance and their views on potential reasons for non-compliance. A reminder email was sent to all after three weeks.

5.2.3. Statistical Analysis

Descriptive statistics (means, proportions) were calculated for responses to both surveys. A chi-squared test was used to test for significant associations between categorical variables. Non-parametric tests were used to compare median number of medications and comorbidities by frequency of use. A 5% level of significance was used for all statistical tests. IBM SPSS for Windows (Version 20) was used for the analysis.
5.3. Results

5.3.1. Patient Survey

67 patients responded to the survey (response rate 74%) and 64% were female. Mean age (SD) of the study group was 75.1 years (11.5), range 45-91 years. Baseline characteristics of the survey population are outlined in table 1. Dizziness was the most frequent indication for prescription of ECS (60%) followed by falls (43%) with 12% of patients unsure. 95% of the patients surveyed were prescribed ECS. 33% of patients wore ECS daily, 13% regularly (1-3 times per week), 11% rarely (1 per week or less) with 43% of patients never wearing them (Figure 1). Over half (51%) of the patients reported difficulty in putting them on, 31% reported discomfort, 13% reported them having no effect on symptoms, 7% disliked their cosmetic appearance, 7% reported interference with choice of clothing and 9% described forgetting to put them on.

Those aged 75 years or older were more likely to report difficulty in application compared to those under 75 (p=0.003). Difficulty in application was also more likely to be reported in those who used ECS rarely or never compared to regular or daily users (p=0.048). Those who wore ECS rarely or never had a median number of comorbidities of 3 compared to 2 for those who wore ECS regularly or daily (p=0.20). Those who wore ECS rarely or never had a median number of medications of 7 compared to 5.5 for those who wore ECS regularly or daily (p=0.07). There was no association between frequency of wear and concomitant prescription of midodrine for OH (p=0.84) or between improvement in symptoms and taking midodrine (p=0.20). More frequent use (regularly or every day) was associated with an improvement in symptoms compared to rare or no use (p=0.001). Of the patients who wore ECS regularly or daily, 69% reported an improvement in symptoms, 28% no change and one patient reported symptoms were worse.
5.3.2. Physician Survey

48 physicians responded (response rate 70%). 89% routinely prescribe ECS for OH. Of those that do not prescribe ECS, (4/69) 8% felt they were not a practical treatment option in this age group while (1/69) 2% did not feel they are of no benefit. 67% of physicians prescribe ECS before commencing pharmacological therapy, 16% at the same time as pharmacological therapy with 16% commencing after pharmacological therapy. 69% of physicians choose thigh length, with 31% using below knee ECS. 22% prescribe class 1 strength ECS with 46% using class 2 and 18% class 3 respectively.

4% of physicians predicted that patients would wear ECS daily, 33% regularly with 56% of physicians feeling patients would wear ECS rarely and 6% never using them at all (Figure 1). There were significant differences between the frequency of use reported by patients and predicted by physicians (p<0.001) with physicians less likely to predict no use or daily use. The most frequent reasons predicted by physicians for less than daily compliance were difficulty with application 87%, discomfort 83% and appearance 42% (Figure 2). Almost half (48%) of physicians agreed that ECS are of benefit in older patients with OH with 31% undecided while 16% of respondents felt ECS are of no benefit. Over half (52%) of physicians that felt ECS are of benefit actually predicted that patients would wear them rarely or never.
**Table 5-1: Patient questionnaire**

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Were compression prescribed for you?</td>
<td>Yes  No</td>
</tr>
<tr>
<td>2: Why were the stockings prescribed to you?</td>
<td>Dizziness  Falls  Unsure</td>
</tr>
<tr>
<td>3: How frequently do you wear them?</td>
<td>Daily  Regularly (1-3 times per week)  Rarely (1 per week or less)  Never</td>
</tr>
<tr>
<td>4: If you are unable to wear them daily, what are the reasons why?</td>
<td>Too hard to put on  Uncomfortable  Appearance  Interferes with my choice of clothing  Unhelpful  Forget to put them on</td>
</tr>
<tr>
<td>5: Overall, what effect have the compression stockings had on your symptoms?</td>
<td>A lot worse  Worse  No change  Better  Made my symptoms go away completely</td>
</tr>
</tbody>
</table>
1: Do you ever prescribe compression stocking for OH?  
   Yes  No
   If no: Why not?
      They are not a practical option in this group
      They do not provide benefit
      Both
2: If Yes: Do you typically prescribe them:
      Before initiating pharmacological therapy
      At the same time as pharmacological therapy
      As an add on to pharmacological therapy
3: What length do you normally prescribe?
   Knee length  Thigh length
4: What compression strength do you typically prescribe?
   Class 1 (12-22 mmHg)  Class 2 (23-32 mmHg)  Class 3 (34-46 mmHg)
5: In your opinion how often do patients actually wear them?
   Daily  Regularly (1-3 times per week)  Rarely (1 per week or less)  Never
6: Among patients who don’t comply, what are the main reasons
   Difficult to put on  Discomfort  Appearance
   Unhelpful  Forget to put them on
7: Based on your experience caring for patients with OH, do you believe that compression are of benefit?
   Disagree strongly  Disagree  Neutral
   Agree  Agree strongly

Table 5-2: Physician questionnaire
<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>24 (36%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>43 (64%)</td>
</tr>
<tr>
<td>Age</td>
<td>45-55 years</td>
<td>6 (9%)</td>
</tr>
<tr>
<td></td>
<td>55-65 years</td>
<td>7 (10%)</td>
</tr>
<tr>
<td></td>
<td>65-75 years</td>
<td>11 (16%)</td>
</tr>
<tr>
<td></td>
<td>75-85 years</td>
<td>36 (54%)</td>
</tr>
<tr>
<td></td>
<td>85-95 years</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Indications</td>
<td>Dizziness</td>
<td>40 (60%)</td>
</tr>
<tr>
<td></td>
<td>Falls</td>
<td>29 (43%)</td>
</tr>
<tr>
<td></td>
<td>Unsure</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Medications</td>
<td>Median number of medications (IQR)</td>
<td>6 (5)</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>2 (3%)</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>30 (45%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Median number of comorbidities (IQR)</td>
<td>2 (1)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>38 (57%)</td>
</tr>
<tr>
<td></td>
<td>Ischaemic Heart Disease</td>
<td>27 (40%)</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>10 (15%)</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td>7 (10%)</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>12 (18%)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>6 (9%)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>8 (12%)</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>7 (10%)</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

Table 1-3: Patient baseline characteristics (n=67 gender, age, indications, medications and comorbidities.)
*Missing data for 4 patients

Figure 5-1: Patient (n=63)* reported and physician (n=48) predicted compliance with ECS
Figure 5-2: Patient (n=63)* reported and physician (n=48) predicted reasons for non-compliance with ECS.

*Missing data for 4 patients
5.4. Discussion

The patient survey revealed that only a third of patients wore ECS daily while over half used them rarely or never, indicating that patients with OH seem either largely committed to ECS, or not at all. Compliance rates with ECS for the treatment of chronic venous insufficiency has demonstrated daily compliance rates from 21%, with the most common reason stated for non-compliance (30%) was non-prescription by the primary physician followed by wear-comfort factors (Raju et al. 2007). Compliance rates in those with chronic venous insufficiency were also shown to increase with increasing duration of symptoms with 40% of patients using them daily between six and ten years. In two surveys of patients prescribed ECS post lower limb thromboembolism, daily compliance of ECS ranged between 74-87% of patients (mean age 61 years in the latter study) wore ECS daily (Kahn et al. 2003; Roche-Nagle et al. 2010). Possible explanations for lower daily compliance with ECS in patients with OH in comparison to those post lower limb thromboembolism may include that this group are more likely to be older with a higher comorbidity burden and concomitant medication usage (Ungar et al. 2006). Analysis of patient demographics were not included in these studies which may limit the understanding of potential factors influencing patient compliance.

In the current study, the mean age of participants was 75.1 years with a median number of two comorbidities and six medications. Older patients were more likely to describe difficulty applying the ECS or described discomfort, limiting their use which is similar to those reasons found in those using ECS for chronic venous insufficiency (Raju et al. 2007). 69% of patients surveyed used five or more medications, the commonly used definition of polypharmacy (Hajjar et al. 2007). Those who wore ECS rarely or never, had a higher median number of medications compared to those who wore ECS regularly or daily. Perceived effect on symptoms had the strongest effect on patient compliance with 69% of regular or daily users reporting an improvement in their symptoms. In studies assessing compliance of ECS in both chronic venous insufficiency and post lower limb thromboembolism symptoms recorded were confined to lower limb swelling or venous ulceration healing, limiting the comparability of effect of symptoms compliance in these studies to an older, heterogenous population such as those with OH.
It is interesting that those patients who were also prescribed pharmacological therapy for OH were no more likely to use ECS more frequently than those who were not. Almost half of our patient group were prescribed pharmacological therapy in addition to ECS and this group did not report an improvement in symptoms. Midodrine and fludrocortisone have both been found to improve orthostatic symptoms in several small studies, however long-term effect of these agents on patient symptoms is unclear (Logan and Witham 2012). Tolerance of postural BP decreases can be variable. Some patients can remain asymptomatic even after a decrease in SBP of 40 mm Hg or more, whereas others become symptomatic even with a SBP above 120 mm Hg (Mathias et al. 1999). The severity of these symptoms largely depends on the vascular supply to target organs including compromise of cerebral blood flow.

The physician survey has several relevant findings. The majority of physicians prescribed ECS for OH, however only fifty percent of respondents reported that they are effective in improving symptoms. This discrepancy between physician views and prescribing practices may be related to the lack of convincing evidence supporting the role of ECS in treating OH, or due to the perception that compliance rates in this group would be low. Most physicians prescribe ECS before pharmacological therapy which indicates a preference for the initial trial of more conservative measures thus potentially avoiding adverse side-effects of medication, which is understandable in this patient group. Although the majority of physicians prescribe thigh length ECS with class 2 strength, there was a lack of consensus regarding the timing of prescription of ECS, length, and compression strength. Physicians correctly identified the main reasons for non-compliance which may be a reflection of issues encountered in their daily clinical practice.

Physicians significantly underestimated the daily compliance rate and those that never use ECS. It has been demonstrated that physicians are poor estimators of patient adherence to a particular treatment with studies of both medications and other treatments reporting correct predictions between 10 to 40% of the time (Parker et al. 2007; Zeller et al. 2008). Patient attitudes regarding adherence to a particular treatment are usually initiated in the medical consultation and accurate prediction of non-adherence is important to identify those that may require further counselling.
A previous study has shown that discussions between physicians and patients regarding patient preferences and lifestyle may improve physicians’ ability to predict non-adherence, which highlights the need for effective communication regarding therapy options and their potential adverse effects (Murri et al. 2002).

The results of this study provide useful information to physicians who prescribe ECS for OH. The patient study group were a well-defined, community based population with information regarding comorbidity and medication usage. The response rates for both surveys were high improving the applicability of results. The current study has several limitations. Firstly, the physicians surveyed were specialists in this subject and the patients included were sampled from a tertiary referral centre for syncope assessment. This may not be representative of the population as a whole. Clinicians in non-specialist units with varying levels of experience managing similar patients may have differing views. Second, we did not have available data on the magnitude or pattern of orthostatic blood pressure decrease from time of diagnosis of OH which may be interesting in future studies to explore associations of compliance with ECS including effect on symptoms. Thirdly, although the majority of the patients included were under active follow-up by the clinical service, some were subsequently discharged, which may have resulted in lower compliance rates in this group.

5.5. Conclusion

Although prescribed frequently, the use ECS in older patients with OH is often limited by issues related to practicality and perceived neutral effect on symptoms. Physicians correctly identified the main reasons for non-compliance however there were significant differences between patient compliance and physician predictions. Further study of alternative and potentially more tolerable non-pharmacological therapeutic strategies for managing OH are warranted.
Chapter 6
Investigating the Potential Benefit of NMES in Older Community Dwelling People with Orthostatic Hypotension – A Feasibility Study

Article submitted to Medical Engineering and Physics April 2015
Abstract published Age and Ageing supplement 2011
6.1. Introduction

Upon assuming the upright posture 500-800 ml of blood may translocate to the lower abdomen, thighs and legs (Smit et al. 1999; van Lieshout et al. 2003). A rise in hydrostatic pressure leads to an initial increase due to filling of the lower limb veins which is followed by a second slower phase due to fluid filtration through capillary walls (Brown and Hainsworth 1999). Occurring simultaneously with gravitationally-induced fluid shifts in the body upon standing, there is an increase in arterial pressure below the heart and a decrease above it (Smit et al. 1999). In healthy individuals, mean arterial pressure (MAP) at carotid level is primarily maintained through rapid activation of neural reflex mechanisms which results in vasoconstriction of the capacitance vessels.

In autonomic failure, there is failure of efficient baroreflex activity and a reduction in blood pressure (BP) may occur upon standing. The change in the hydrostatic gradient experienced on transition from supine to standing can lead to subsequent cerebral hypoperfusion and symptoms including, dizziness, visual disturbances and loss of consciousness (Brown and Hainsworth 1999). As blood pools in in the venous system at and below the level of the trunk there is a resultant fall in venous return to the heart and reduction in central venous pressure with a consequent decrease in cardiac filling, stroke volume (SV) and cardiac output (CO) with compensatory increase in heart rate (HR). Treatment strategies for orthostatic hypotension (OH) in an older population can be particularly challenging. Drug treatment can frequently limited by side effects such as fluid retention or supine hypertension with non-pharmacological strategies commonly compromised by issues related to practicality (Logan and Witham 2012).

Over recent years, Neuromuscular Electrical Stimulation (NMES) has been increasingly used in rehabilitative settings to improve muscle function, prevent muscle atrophy, improve motor recovery and increase motor strength. Activation of the calf muscle pump leads to compression of the intramuscular veins resulting in raised venous pressure and venous return to the heart preventing pooling of blood in the legs (Valic et al. 2005). Lower limb NMES administered for blood flow assist purposes has demonstrated positive haemodynamic responses in healthy subjects and
patients with chronic venous insufficiency (Lyons et al. 2002; Clarke Moloney et al. 2006). NMES has been shown to attenuate the BP drop in patients with longstanding spinal cord injury (SCI) and OH as a consequence (Sampson et al. 2000; Chi et al. 2008).

It was hypothesised that application of NMES to the calf muscles of older community-dwelling patients with OH may increase venous return and attenuate orthostatic blood pressure reductions. A feasibility study was performed to test this hypothesis with a secondary objective of determining the optimal NMES setting for this purpose.
6.2. Methods

6.2.1. Study Design

Randomised cross-over design incorporating two protocols

6.2.2. Participants

Community-dwelling subjects aged 65 years or older with a history of OH were recruited as described in 4.2.

6.2.3. Inclusion Criteria

Age 65 years or greater
Diagnostic OH as per consensus criteria

6.2.4. Exclusion Criteria

Current use of psychotropic medications
Current pharmacological treatment for OH including midodrine, fludrocortisone or droxidopa
Recent (<6 months) myocardial infarction / stroke
Clinical evidence of hypovolaemia
Permanent Pacemaker
Total knee replacement
Peripheral vascular disease
Significant cardio-respiratory disease

6.2.5. Head-Up Tilt Protocol

Head-up tilt (HUT) testing was performed using standardised conditions in accordance with the 1996 expert consensus document for all patients. OH was defined as a reduction in SBP of >20 mmHg and/or DBP of >10 mmHg (Brignole, Alboni, Benditt, Bergfeldt, Blanc, Bloch Thomsen, et al. 2004). The protocol is described in 4.8.
The first three subjects completed a two HUT protocol which included a control HUT and a HUT with either alternate leg or simultaneous leg NMES settings. The order (control or intervention) was randomised. Following this, it was decided to alter the study design to include a three HUT protocol with the remaining subjects completing a three HUT protocol (i.e., control, alternate and simultaneous NMES settings). Randomisation was carried out using a closed envelope randomisation technique.

6.2.6. Electrical stimulation protocol

NMES was applied using a custom built, two channel stimulator (Duo-STIM, Bioelectrics Research Cluster, NUI Galway) and discussed in 4.10. The protocol is outlined in 4.11.

6.2.7. Statistical Analysis

The distribution of data for change in outcome across experimental groups was tested for normality. Summary measures are presented as median (interquartile range) for skewed data. As this is a pilot study, the analysis was descriptive and used to inform a sample size calculation for a larger study. Non-parametric tests for related samples were used to test for significant differences across groups for each outcome but the tests were used only to identify possible patterns in the data across groups and no adjustment was made for multiple testing.
6.3. Results

Fourteen subjects were recruited. One was excluded due to presence of a permanent pacemaker which was not disclosed at the time of recruitment, while another was unable to complete the study protocol due to chronic shoulder discomfort, see study flow figure 1. Of the twelve participants who completed the study, ten were male. The median age was 76.5 years (range 71–90). One was underweight (BMI<18.5), two were normal weight, eight were overweight and one was obese (BMI≥30). Three of the twelve participants had hypertension. The median number of medications for participants was two. Demographic data are outlined in Table 6-1. Mean NMES intensity was 50% of maximal stimulation intensity for both legs (IQR 45-55).

Of the study group, eleven had reproducible OH by diagnostic criteria. The change in outcomes by group are summarised in Table 6-2. The alternate leg intervention had a smaller median reduction in systolic blood pressure (SBP) (-16 mmHg) compared to the control group (-21 mmHg) (p=0.48). The median reduction in systolic blood pressure SBP was similar for the control and simultaneous intervention (-22.5 mmHg) (p=0.72). The median reduction in diastolic blood pressure (DBP) were similar for the three groups with -6 mmHg in the simultaneous group, -8 mmHg in the alternate and -8.5 mmHg in the control group respectively, see Figures.

There was a general pattern for less variation in the change for each outcome in the alternate intervention compared to the control and simultaneous intervention. A smaller change in HR was observed in both the alternate (p=0.08) and simultaneous group compared to the control (p=0.13). SV and CO were increased for the alternate leg NMES group compared to the control group (p=0.06 and p=0.16 respectively).
14 Recruited

12 Study Group

2 Excluded

3 Subjects: Protocol One
Control HUT
Alternate NMES HUT
OR
Simultaneous NMES HUT

9 Subjects: Protocol Two
Control HUT
Alternate NMES HUT
Simultaneous NMES HUT

Figure 6-1: Study flow
<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>BMI</th>
<th>Co-morbidities</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70-74</td>
<td>24.5</td>
<td>Osteopenia, OA, Hyperlipidaemia</td>
<td>Statin, Ca2+D3</td>
</tr>
<tr>
<td>2</td>
<td>70-74</td>
<td>29.8</td>
<td>Hypertension</td>
<td>ARB, Beta blocker</td>
</tr>
<tr>
<td>3</td>
<td>80-84</td>
<td>26.1</td>
<td>Depression, Hypertension</td>
<td>ACE, SSRI</td>
</tr>
<tr>
<td>4</td>
<td>75-79</td>
<td>29.3</td>
<td>Osteopenia</td>
<td>Ca2+D3</td>
</tr>
<tr>
<td>5</td>
<td>70-74</td>
<td>30.1</td>
<td>OA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>90-94</td>
<td>26.8</td>
<td>Hypertension</td>
<td>ACE, Aspirin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Beta blocker</td>
</tr>
<tr>
<td>7</td>
<td>70-74</td>
<td>28.1</td>
<td>Osteopenia</td>
<td>Ca2+D3</td>
</tr>
<tr>
<td>8</td>
<td>80-84</td>
<td>17.5</td>
<td>Depression, CLL</td>
<td>Aspirin, SSRI</td>
</tr>
<tr>
<td>9</td>
<td>80-84</td>
<td>29</td>
<td>Osteoporosis, Hyperlipidaemia</td>
<td>Bisphosphonate, Statin</td>
</tr>
<tr>
<td>10</td>
<td>75-79</td>
<td>27.5</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>11</td>
<td>70-74</td>
<td>29.1</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>12</td>
<td>75-79</td>
<td>22.8</td>
<td>Depression, Hyperlipidaemia</td>
<td>Statin, SSRI</td>
</tr>
</tbody>
</table>

Table 6-1: Subject demographics
ACE-angiotensin converting enzyme, ARB-angiotensin receptor blocker, SSRI-selective serotonin receptor, CLL-chronic lymphocytic leukaemia, OA-osteoarthritis, Ca2+D3-calcium vitamin D3
<table>
<thead>
<tr>
<th></th>
<th>Control (n=13)</th>
<th>Alternate (n=11)</th>
<th>NMES (n=10)</th>
<th>Simultaneous NMES (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in SBP</td>
<td>-21.0 (18)</td>
<td>-16.0 (15)</td>
<td>-22.5 (25)</td>
<td></td>
</tr>
<tr>
<td>Change in DBP</td>
<td>-8.5 (15)</td>
<td>-8.0 (8)</td>
<td>-6.0 (14)</td>
<td></td>
</tr>
<tr>
<td>Change in HR</td>
<td>4.0 (7)</td>
<td>1 (10)</td>
<td>1.0 (7)</td>
<td></td>
</tr>
<tr>
<td>Change in SV</td>
<td>-8.0 (22)</td>
<td>6.5 (20)</td>
<td>-1.7 (25)</td>
<td></td>
</tr>
<tr>
<td>Change in TPR</td>
<td>-0.13 (0.35)</td>
<td>-0.19 (0.19)</td>
<td>0.11 (0.76)</td>
<td></td>
</tr>
<tr>
<td>Change in CO</td>
<td>-0.04 (1.34)</td>
<td>0.56 (0.93)</td>
<td>-0.02 (1.78)</td>
<td></td>
</tr>
</tbody>
</table>

Table 6-2: Median (Interquartile range) change for each outcome by group
Figure 6-2: Change in SBP by group
Figure 6-3: Change in DBP by group
Figure 6-4: Change in HR by group
Figure 6-5: Change in SV by group
Figure 6-6: Change in TPR by group
Figure 6-7: Change in CO by group
6.4. Discussion

To our knowledge, this is the first study to report on the effect of calf muscle NMES in a cohort of community dwelling older subjects with OH. A trend towards benefit using NMES in attenuating OH was demonstrated with the alternate NMES setting resulting in the smallest SBP reduction and largest increases in CO and SV in comparison to the control and simultaneous leg NMES intervention.

It has been previously demonstrated that NMES-induced contractions of the leg muscles increases CO, SV, and venous return in subjects with autonomic dysfunction following SCI (Raymond et al. 1999; Faghri and Yount 2002). Increases in ventricular filling and left ventricular end-diastolic volume may augment CO resulting in an increase in arterial BP (Davis et al. 1990). The effect of this increased preload stretch is an increase in ventricular contractility with simultaneous increases in SV and SBP. In a study by Sampson et al. which incorporated two HUT sessions, the quadriceps and pretibial muscles or the patellae and malleoli were stimulated using a 50 Hz, 250 µs wave form with currents up to 160 mA (Sampson et al. 2000). SBP increases were recorded regardless of the stimulation site used. The rise in BP was proportional to increasing stimulation amplitude but stabilised after 96 mA. In a study of patients with chronic SCI, NMES of leg muscles was shown to increase CO and SV in 6 men with paraplegia, while performing arm-crank exercise at maximal effort (Davis et al. 1990). Another study using asynchronous NMES stimulating both knee extensors and plantar flexors in subjects with acute SCI demonstrated an attenuation in SBP drop and HR rise following progressive tilt rise in the treatment group (Elokda et al. 2000).

In the present study, the outcome variables of SBP, DBP, HR, and Modeflow derivations of CO, SV and TPR were used to assess treatment efficacy. Alternate leg NMES demonstrated the smallest drop in SBP in comparison to the control and simultaneous NMES setting. An increase in CO and SV was recorded with reductions in TPR and HR which is consistent with the effect of NMES in other studies in those with SCI (Elokda et al. 2000; Davis et al. 1990; Raymond et al. 1999). It is thought that the haemodynamic effects of NMES on patients following SCI may be related to autonomic dysreflexia dependent on the level of spinal
compromise and the augmentation in BP is sustained for only a short period of time before returning to baseline levels. Although the population in this study were healthy subjects with OH and differed significantly from those with significant autonomic dysfunction with spinal cord injury in previous studies, the effect of alternate leg NMES seems to be similar.

It is more difficult to explain the effect of simultaneous leg NMES on haemodynamic parameters. There was a modest attenuation of DBP drop, minimal effect on SBP, slight increase in TPR and reductions in SV and CO. As simultaneous stimulation involves the synchronous contraction of both calf muscles, this may pose different physiological considerations. This may be comparable to the effect of simultaneous activation of lower limb muscle pumps seen when standing up from a sitting position. Possible explanations for the limited effect of this pattern of stimulation on haemodynamic parameters could be related to a combination of the following factors (Rossberg and Penaz 1988; Convertino et al. 1998; Wieling et al. 2007). Firstly, decompression of the venous vessels may lead to an increase in the arterio-venous pressure gradient that can result in relative tissue hypoxia. Second, induced ischemia in the leg muscles may augment the fall in arterial resistance by local factors similar in theory to the post-tourniquet effect, leading to increased microvascular permeability. Thirdly, the muscle activity during the simultaneous stimulation promotes venous return, which can trigger cardiopulmonary pressure receptors and leading to a transient decrease of sympathetic vasoconstrictor outflow, resulting in lower BP. In the circumstances outlined, a reduction in peripheral TPR is usually seen, however in the simultaneous stimulation group TPR was slightly increased which is in contrast to previous studies.

The current study has several limitations. Firstly, the study sample size is small and the results may not be generalizable. However, as this is a feasibility study, the analysis was descriptive and used to inform a sample size calculation for a larger study potentially yielding more reliable results. Secondly, the majority of participants were overweight which may have negatively influenced the efficacy of NMES. The study protocol utilised an identical, standard sized electrode for all participants. Excessive subcutaneous adipose tissue has been previously demonstrated to be an important limiting factor in the conduction of current from the
skin to the target motor neurons which is due to its higher electrical resitivity and lower blood flow (Miller et al. 2008). In view of this, higher stimulus currents are required to evoke muscle contraction in overweight subjects than in subjects of a healthy weight which may lead to patient discomfort and intolerance of the therapy (Lyons et al. 2004). Larger electrodes may overcome this issue clinically and, reduce the current density at the skin surface (Petrofsky 2008). Thirdly, the present study design did not include an objective assessment of subject tolerance of NMES or the potential effect on symptomatology which would be important in future studies to determine whether NMES may be an effective and practical treatment option in older subjects with OH.

6.5. Conclusion

NMES may be useful in attenuating BP reductions in older healthy subjects with OH with alternate leg NMES setting demonstrating the smallest SBP drop. A larger sample size, further objective measurements of tolerance, effect on symptoms and haemodynamic change are needed to confirm the potential efficacy and practicality of using calf muscle NMES in this population.
Chapter 7

Tolerability and Haemodynamic Effects of NMES in Young Healthy Individuals During Passive Orthostatic Challenge

Manuscript in preparation
7.1. Introduction

During clinical use, muscle fatigue and reduced tolerability of NMES are usually the main limiting factors (Jubeau et al. 2008). Initial development and implementation of neuromuscular electrical stimulation (NMES) devices as a therapeutic modality were often limited by discomfort. In an early study investigating the effect of NMES on preventing lower limb venous thrombosis in a post-operative surgical group, effective NMES contraction could only be obtained when the patient was under light anaesthetic (Browse and Negus 1970). Early NMES applications employed monophasic waveforms which are capable of altering ionic distributions leading to depolarisation which could result in skin damage including burns. The development of microcontrollers in the design of NMES devices over recent years has facilitated the implementation of accurately controlled waveforms and novel algorithms (Broderick et al. 2008) which have significantly increased the comfort and tolerance of NMES users. The advent of biphasic waveforms which can be either asymmetric or symmetric has minimised ion redistribution and the subsequent risk of skin disturbance.

Several studies have previously examined patient perceptions of NMES. A study of the effects of NMES following four hours of bed rest in healthy participants who underwent a four hour stimulation protocol (Broderick et al. 2010) found NMES to be well tolerated when assessed by a visual analogue scale (VAS). At the end of the study protocol, two participant’s scores increased from mild to moderate discomfort, while two other participant’s scores decreased to mild, with the remainder unchanged. In another study of forty nine healthy subjects, each participant who received calf muscle NMES was asked to complete a questionnaire regarding the acceptance of NMES. Both groups found NMES to be comfortable and strongly felt that NMES would be an acceptable form of treatment if directed by their physician (Kaplan et al. 2002). In a study of twenty four healthy participants evaluating the use of a week-long protocol with 1.5 hours of NMES daily in conjunction with compression therapy demonstrated sustained increased popliteal venous blood flow in the NMES group, progressively increasing intensity of stimulation with a reduction in perceived discomfort and no reported adverse effects (Corley et al. 2012).
The effect of four different electrode sizes on several excitatory responses were studied in twenty healthy participants and concluded that the size of the electrode affects the stimulus parameters, comfort, and force generation associated with electrically induced excitatory responses (Alon et al. 1994). Another study assessed the comfort associated with and without NMES in ten patients with chronic venous insufficiency using a VAS (Clarke Moloney et al. 2006), and found that the comfort categorical rating remained unchanged in all but one patient.

The feasibility study presented in chapter six concluded that calf muscle NMES may be useful in attenuating the drop in blood pressure (BP) in older subjects with OH, with the alternate leg NMES setting demonstrating the most favourable haemodynamic response. This study aimed to assess tolerance and acceptability of both simultaneous and alternate leg NMES settings in a young, healthy population during passive orthostatic challenge. A secondary objective was to assess the effect of both calf muscle NMES settings on haemodynamic parameters in this group.
7.2. Methods

7.2.1. Study Design
Randomised crossover

7.2.2. Subjects
A convenience sample of healthy subjects (n=14) were recruited who worked in the affiliated medical department. A member of the investigation team initially examined each subject to ensure they satisfied the inclusion and exclusion criteria. The inclusion and exclusion criteria are outlined in 4.4.

7.2.3. Inclusion Criteria
Age 20-40 years

7.2.4. Exclusion Criteria
Current smoker
Current use of oral contraceptive pill
Pregnancy
Clinical evidence of hypovolaemia

7.2.5. Tilt Protocol
Head-Up Tilt (HUT) testing was performed using standardised conditions in accordance with the 1996 expert consensus document for all patients as described in 4.8.

7.2.6. Electrical Stimulation Protocol
NMES was applied using a custom built, two channel stimulator (Duo-STIM, Bioelectrics Research Cluster, NUI Galway). The protocol is outlined in 4.11.
7.2.7. Duplex Scanning

Duplex ultrasound was used to monitor the subjects’ lower limb haemodynamic response during each intervention using a Siemens Sonoline Sienna® ultrasound machine with a broadband array probe (Frequency 5–13 MHz). The protocol is discussed in 4.12.3.

7.2.8. Comfort Evaluation Procedure

Comfort was assessed by asking subjects to mark their level of comfort using a 100 mm, non-hatched visual-analogue scale (VAS) at 2 time points (just after set-up of the NMES and at the end of the protocol). This is summarised in 4.14.

7.2.9. Symptom Recording

Subjects were asked to mark their level of symptoms encountered during the HUT using a 100 mm, non-hatched visual-analogue scale (VAS) once the tilt table had returned to the horizontal position as in 4.13.

7.2.10. Statistical analysis

Categorical data were summarised using frequencies and percentages. The distribution of numeric data were tested for normality using normality tests. Mean (SD) are presented for normally distributed data and median (range) for non-normally distributed data. Repeated –measures ANOVA was used to test for significant differences in haemodynamic parameters between groups (control, alternate and simultaneous). Contrasts were used for pairwise comparisons. Non-parametric tests for related samples were used to compare median VAS ratings. A 5% level of significance was used for all tests and the statistical software package SPSS Version 21 for Windows was used for the statistical analysis.
7.3. Results

The mean age of the subjects was twenty nine years (range 26-32). Ten (71%) of the subjects were male and eleven (79%) had a BMI in the normal range 18.5 to 24.9. Three subjects had a BMI in the overweight range 25-29.9. The median stimulation intensity was 40% of maximal (IQR 35-46) for both legs.

7.3.1. Tolerability

Thirteen of the fourteen subjects indicated that they would consider NMES as an acceptable form of treatment. Ten (71%) described the sensation as comfortable with the remaining four subjects describing it as bearable. Twelve (86%) expressed a preference for the alternate over simultaneous leg NMES setting. The subject who indicated that NMES was not an acceptable form of treatment described the sensation as bearable and expressed a preference for the asynchronous setting.

Pain levels at initial setup were low with a median of 7 (range 0 to 59) on a scale of 0 to 100. Eleven of fourteen subjects had pain levels categorised as mild (0-30) with the remaining three subjects in the moderate pain category (30-60). There was a small reduction in pain levels after the protocol was completed with a median of 6 (range 0 to 21) for pain levels after the protocol and all subjects were in the mild pain category (table 1).

The degree of symptoms recorded was low for all three groups with a median of 3 for the control tilt (range 0-32); a median of 4 for the simultaneous setting (range 0-32) and a median of 2 for the alternate setting (range 0-13). The rating of symptoms was significantly different between the three groups (p=0.01).
7.3.2. Haemodynamic parameters

Table 2 summarises the haemodynamic parameters for the control HUT, alternate and simultaneous leg NMES setting. The smallest changes in SBP, DBP, HR and MAP were recorded for the alternate NMES setting. Venous flow (VF) and peak systolic velocity (PSV) were highest on average for the alternate setting. Significant differences were observed for systolic blood pressure (SBP), heart rate (HR), VF and PSV across the three groups (Table 2, Figures 1-4). Pairwise comparisons for the alternate and simultaneous settings showed no significant differences between the two groups.
<table>
<thead>
<tr>
<th>Subject</th>
<th>Initial VAS scores (mm)</th>
<th>Initial Pain category</th>
<th>Final VAS scores (mm)</th>
<th>Final Pain category</th>
<th>Difference in VAS scores (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>Mild</td>
<td>15</td>
<td>Mild</td>
<td>15 &gt;MCSD</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Mild</td>
<td>4</td>
<td>Mild</td>
<td>-2</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Mild</td>
<td>0</td>
<td>Mild</td>
<td>-2</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Mild</td>
<td>5</td>
<td>Mild</td>
<td>4</td>
</tr>
<tr>
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<td>4</td>
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<td>-1</td>
</tr>
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<td>6</td>
<td>25</td>
<td>Mild</td>
<td>7</td>
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<td>-18</td>
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<td>0</td>
<td>Mild</td>
<td>-6</td>
</tr>
<tr>
<td>8</td>
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<td>Mild</td>
<td>9</td>
<td>Mild</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>Mild</td>
<td>17</td>
<td>Mild</td>
<td>-1</td>
</tr>
<tr>
<td>10</td>
<td>59</td>
<td>Moderate</td>
<td>3</td>
<td>Mild</td>
<td>-56</td>
</tr>
<tr>
<td>11</td>
<td>0</td>
<td>Mild</td>
<td>0</td>
<td>Mild</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>48</td>
<td>Moderate</td>
<td>21</td>
<td>Mild</td>
<td>-27</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>Moderate</td>
<td>12</td>
<td>Mild</td>
<td>-22</td>
</tr>
<tr>
<td>14</td>
<td>18</td>
<td>Mild</td>
<td>16</td>
<td>Mild</td>
<td>-2</td>
</tr>
</tbody>
</table>

Table 7-1: VAS scores, pain category and the difference in scores before (initial) and during (final) NMES application.
<table>
<thead>
<tr>
<th></th>
<th>Control Mean (SD)</th>
<th>Alternate NMES Mean (SD)</th>
<th>Simultaneous NMES Mean (SD)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in systolic BP</td>
<td>-18.9 (16.7)</td>
<td>-11.7 (13.1)</td>
<td>-14.2 (13.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in diastolic BP</td>
<td>-15.4 (14.1)</td>
<td>-10.0 (10.5)</td>
<td>-12.4 (8.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Change in HR</td>
<td>8.3 (13.8)</td>
<td>0.36 (10.0)</td>
<td>2.6 (9.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Change in SV</td>
<td>-0.27 (28.0)</td>
<td>-2.1 (20.6)</td>
<td>-0.03 (18.2)</td>
<td>0.96</td>
</tr>
<tr>
<td>Change in TPR</td>
<td>0.05 (0.46)</td>
<td>-0.08 (0.23)</td>
<td>-0.13 (0.39)</td>
<td>0.47</td>
</tr>
<tr>
<td>Change in CO</td>
<td>-0.70 (1.65)</td>
<td>0.24 (0.83)</td>
<td>0.01 (1.58)</td>
<td>0.13</td>
</tr>
<tr>
<td>Venous flow</td>
<td>49.0 (13.2)</td>
<td>143.0 (50.5)</td>
<td>140.5 (61.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak systolic velocity</td>
<td>6.9 (2.1)</td>
<td>29.0 (8.9)</td>
<td>28.5 (8.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 7-2: Haemodynamic parameters by group (n=14)

*P-value from repeated measures ANOVA for the three groups
Figure 7-1: Venous flow volume measurements due to the NMES elicited calf muscle contraction
Figure 7-2: Peak venous blood flow velocity measurements due to the NMES elicited calf muscle contraction
Figure 7-3: Change in SBP by group
Figure 7-4: Change in HR by group
7.4 Discussion

This study has shown that the use of calf muscle NMES during passive orthostatic challenge in a healthy younger group is well tolerated. The majority of subjects describe the sensation as comfortable and consider it an acceptable form of treatment. Most subjects described an improvement in comfort when assessed at the end of the protocol. The alternate leg NMES setting was preferred, while also demonstrating the most positive effect on haemodynamic parameters.

The present study used a relatively short protocol of three minutes for each passive orthostatic change resulting in a total of six minutes stimulation duration in total. VAS scores did not increase indicating perceived discomfort which is in keeping with earlier studies of healthy subjects and patients post orthopaedic hip surgery (Broderick et al. 2010, 2011, 2013; Corley et al. 2012). Previous studies evaluating lower limb NMES tolerability have generally involved longer study protocols (Kaplan et al. 2002; Clarke Moloney et al. 2006; Broderick et al. 2010; Corley et al. 2012; Vivodtzev et al. 2012). These have included individual sessions lasting from up to four hours in isolation or daily sessions of up to forty five minutes each day over a six week period which may involve a degree of conditioning of the stimulated muscle and potentially less discomfort perceived.

During NMES, the activation of skin surface sensory receptors “can be minimized through the use of advanced skin surface electrodes, correct electrode placement and biphasic stimulation waveforms known to be more comfortable” (Pambianco et al. 1995). It has been shown that obese subjects require greater levels of stimulation since the current has to pass through the adipose layer before it can reach the muscle and cause a contraction (Alon and V Smith 2005). Another study demonstrated higher NMES amplitudes necessary to produce at least 30% of maximal isometric contractions of the quadriceps in subjects with thicker skinfolds (Miller et al. 2008). Male subjects experience less pain and can tolerate higher levels of stimulation intensity than females (Clarke Moloney et al. 2006; Maffiuletti et al. 2008).

During NMES training it has been shown that increasing stimulation intensity is crucial to the success of the intervention in terms of improving muscle function and
functional capacity in a rehabilitation setting (Theurel et al. 2007). In a randomised, double-blind controlled study of twenty two patients with COPD, five days per week over a six week period, those who could not increase NMES current intensity by more than 10 mA or could not reach 30 mA of current intensity during a six week program did not exhibit improvement in muscle function and exercise tolerance (Vivodtzev et al. 2012). In the present study, the stimulation intensity was determined following the initial set-up and was not modified thereafter with a median stimulation intensity of 40% of maximal intensity which compares favourably with the published literature.

The reasons for inter-individual variation in the tolerance to NMES remain unclear, although several theories exist. The magnitude of cardiac and ventilator demands during NMES may be important. Up to a two-fold increase in resting cardiorespiratory parameters values may be expected depending on the stimulation intensity compared to voluntary contraction (Theurel et al. 2007), which reflects the differences in motor recruitment between NMES and voluntary contractions. Another study of fifteen patients with COPD and nine aged matched healthy controls evaluating the effect of NMES on exercise tolerance in patients with COPD demonstrated that electrically-induced leg muscle fatigue reduced tolerance to NMES (Gagnon et al. 2009). The presence of a systemic inflammatory response following electrical stimulation could influence the tolerance to NMES. An increase in plasma IL-6 levels was seen in thirteen out of twenty patients after one NMES session lasting forty five minutes in patients with COPD (Vivodtzev et al. 2014). Similar observation are seen in rodent and human studies which have found that repeated muscle contractions induced by electrical current (Jonsdottir et al. 2000) or during whole body exercise is associated with elevated IL-6 (Van Helvoort et al. 2006).

In the present study, the PSV was 29 cm/s in the alternate leg NMES group and 28.5 cm/s in the simultaneous NMES group compared to 6.9 cm/s in the control group which is consistent with previous studies. The alternate leg NMES setting demonstrated the most favourable response in attenuating the SBP decrease and increase in HR which is similar to the results seen in the feasibility study of older subjects with OH in chapter six. In recent years, improvements in lower limb venous
blood flow have been demonstrated in healthy subjects with calf NMES resulting in peak systolic velocities of 13-120 cm/s in the popliteal vein (Clarke Moloney et al. 2006; Griffin et al. 2010), with our results comparing favourably.

This study has several limitations. Firstly, the study group were a convenience sample of young healthy participants who worked in a busy medical department. The protocol was undertaken between 9am and 5pm with those in the afternoon potentially at higher risk of experiencing hypovolaemia which would contribute to BP reductions, despite normal clinical examination prior to the study. There were no objective measures of fluid volume status included which may be useful in future studies evaluating the effect of NMES on older subjects with OH. Second, as the study population included only young, healthy subjects it is not surprising that orthostatic symptoms were not encountered during a passive orthostatic challenge. The inclusion of an active orthostatic challenge should be considered to establish the effect of NMES in further studies as this includes natural activation of the calf muscle pump which may have additional effects on total peripheral resistance and possibly resulting in larger decreases in systemic BP which may exacerbate orthostatic symptoms.

7.5 Conclusion

NMES is well tolerated in a young healthy population undergoing orthostatic challenge, with subject preference and haemodynamic response favouring the alternate setting. This should prompt further study of this application in an older population with OH to include both active and passive orthostatic challenges with an assessment of tolerability and effect on symptoms.
Chapter 8
Comparison of NMES and Compression Stockings in a Community Dwelling Older Population with Orthostatic Hypotension During Active and Passive Orthostatic Challenges – A Randomised Crossover Study

Abstract accepted British Geriatric Spring Meeting 2015
Manuscript in preparation
8.1. Introduction

NMES is defined as the application of an electrical stimulus to motor points in the body using electrodes placed on the surface of the skin in order to elicit muscular contraction. Calf muscle activation compresses the intramuscular and surrounding veins, which raises venous pressure and forces blood back toward the heart preventing pooling and stagnation of blood in the lower limbs (Valic et al. 2005). NMES administered for blood flow assist applications has demonstrated favourable haemodynamic responses in healthy subjects and patients with chronic venous disease (Clarke Moloney et al. 2006). Lower limb extremity NMES has been shown to attenuate the BP drop in patients with longstanding spinal cord injury (SCI) who developed OH (Sampson et al. 2000; Faghri and Yount 2002).

Elastic compression stockings (ECS) are commonly used for those affected by recurrent OI and. Up to 800 ml of blood can translocate into the lower limbs following several minutes in the upright posture (Privett et al. 2010). The rationale of using graduated compression garments is to apply external counter-pressure to the lower limbs or abdomen with the effect of reducing venous pooling and capillary filtration resulting in increased venous return (Brown and Hainsworth 1999). Short term improvements in orthostatic BP with garments applying counter-pressure to lower limbs have been demonstrated (Privett et al. 2010). Garments that compress the abdomen have shown greater promise in those with OH (Podoleanu et al. 2006), although these may be less practical in an older age group.

The feasibility study presented in chapter six concluded that NMES may be useful in attenuating the drop in BP in older subjects with OH, with the alternate leg NMES setting demonstrating the most favourable haemodynamic response. Alternate leg calf muscle NMES was shown to result in the most favourable haemodynamic pattern and most tolerable in a group of healthy, younger participants in chapter seven. This study aimed to compare the haemodynamic effect of alternate leg calf muscle NMES with ECS using both passive and active orthostatic challenges. We aimed to record objective measures of venous blood flow and effect of each intervention on symptoms in response to each intervention. A secondary objective was to evaluate tolerability of alternate leg calf muscle NMES in this group.
8.2. Methods

8.2.1. Study Design

The study incorporated two protocols evaluating head-up-tilt (HUT) and active stand (AS) orthostatic stressors each of randomised cross-over design (see figure 8-1 and 8-2). There were three interventions in each protocol including control, NMES and ECS. Each protocol was performed at the same time on successive days for the majority of participants. The order of intervention was determined using closed envelope randomisation technique.

Figure 8-1: Protocol 1 illustrating three HUT protocol with control, NMES and ECS interventions

Figure 8-2: Protocol 2 illustrating three active stand protocol with control, compression and NMES interventions
8.2.2. Participants

40 community dwelling subjects with a confirmed history of OH were recruited. These were identified from HUT files stored in a computerised database generated following their participation in the Health Inequalities and Ageing in the Community Study (HIACE) as discussed in 4.2.

8.2.3. Inclusion Criteria

Age 65 years or greater
Diagnostic OH as per consensus criteria from HIACE database

8.2.4. Exclusion Criteria

Current use of psychotropic medications
Current pharmacological treatment for OH including midodrine, fludrocortisone or droxidopa
Recent (<6 months) myocardial infarction / stroke
Permanent Pacemaker
Total knee replacement
Peripheral vascular disease
Significant cardio-respiratory disease

8.2.5. HUT Protocol

HUT testing was performed using standardised conditions in accordance with the 1996 expert consensus document for all patients as outlined in 4.8. The HUT study protocol included asynchronous NMES, ECS and control.

8.2.6. Active Stand Protocol

The active stand study protocol included asynchronous NMES, ECS and control interventions performed in the same order as in the tilt protocol on successive days. The active stand protocol is outlined in 4.9.
8.2.7. Electrical Stimulation Protocol

NMES was applied using a custom built, two channel stimulator (Duo-STIM, Bioelectrics Research Cluster, NUI Galway) as described in 4.10. Alternate leg NMES was used as outlined in 4.11.

8.2.8. Duplex Scanning

Duplex ultrasound was used to monitor the subjects’ lower limb haemodynamic response during each intervention using a Siemens Sonoline Sienna® ultrasound machine with a broadband array probe (Frequency 5–13 MHz). A single examiner recorded responses for each intervention. The protocol is discussed in 4.12.

8.2.9. Elastic Compression Stockings

Thigh length class 3 ECS (34-46 mmHg) were used (Medivan®). The ECS were applied by research staff with each subject lying supine during the five minute rest period between interventions as discussed in. Baseline haemodynamic HR and BP traces were obtained prior to onset of intervention.

8.2.10. Sub-Compression Stocking Pressure Recording

Sub-elastic compression pressure was measured with an electronic manometer (Kikuhime® TT Medi Trade, Soledet 15, DK 4180 Soro) as outlined in 4.13.

8.2.11. Comfort evaluation procedure

Comfort was assessed by asking subjects to mark their level of comfort using a 100 mm, non-hatched visual-analogue scale (VAS) at 2 time points (just after set-up of the NMES and at the end of the protocol). This is summarised in 4.14.
8.2.12. Symptom recording

Subjects were asked to mark their level of symptoms encountered during the HUT using a 100 mm, non-hatched visual-analogue scale (VAS) once the tilt table had returned to the supine position as outlined in 4.15.

8.2.13. Statistical Analysis

Numeric variables were tested for normality and are summarised as mean (standard deviation) for normally distributed variables or median (range or interquartile range) for non-normally distributed variables. A repeated-measures ANOVA with two within-subject factors (intervention with three levels and protocol with two levels) was used to test for significant differences in haemodynamic parameters and symptom evaluation by intervention and protocol. The interaction between intervention and protocol factors was also tested and simple contrasts were used to compare levels of each factor. Log transformed data were used in the ANOVA for non-normally distributed variables. McNemar’s test was used to compare paired proportions classified as arteriolar or not within protocols. A significance level of 5% was used for all statistical tests and the analysis was carried out using SPSS Version 21 for Windows.
8.3. Results

Forty subjects were recruited with thirty eight included in the analysis. Two HUT files were not of sufficient quality to enable analysis and were thus excluded. The mean age of the study group was 74.5 years (SD 3.96, range 71 to 90). Of the 38 subjects, 27 (71%) were female. 22 (58%) were overweight and 6 (16%) were obese. The median number of medications per subject was 2 (range 0 to 7) with 7 (18.5%) patients on five or more medications and three subjects (8%) not on any medication. The median number of comorbidities per subject was 2 (range 0 to 4). 22 subjects (58%) were hypertensive.

Table 1 summarises stocking size, calf diameter, sub-bandage pressure and stimulation intensity for the subjects. Size 4 class 3 ECS were most commonly used (47.4%) followed by size 3 (34.2%). Mean sub-ECS pressure was 47.3 mmHg which is slightly above factory recommendation of 34-46 mmHg. Table 2 summarises the haemodynamic parameters and symptom evaluation by intervention and protocol. Both intervention and protocol were significant factors in predicting mean change in SBP and mean peak systolic velocity (Table 2). There was a significant interaction effect between intervention and protocol for mean change in SBP (p=0.02) indicating that the effect of intervention differed across protocols.

Pairwise comparisons demonstrated a significant difference in mean change in systolic blood pressure between the control and the NMES interventions in both the HUT and active stand protocols (p=0.01 and p=0.03 respectively) but not between the ECS and the NMES interventions in either protocol (Table 1). There was a significant difference in mean peak systolic velocity between the control and the NMES (p<0.001) and also between the ECS tilt and the NMES interventions (p<0.001) in both protocols. There was a significant difference in mean venous blood flow between the control and the NMES (p<0.001) and also between the ECS and the NMES interventions (p<0.001) in both protocols.

There was a significant difference in evaluation of symptoms between the control and the NMES interventions in both protocols (p=0.002 and p=0.01 respectively) however there was no difference between the ECS tilt and the NMES interventions.
in either protocol. There were no significant differences in mean change in DBP or HR by intervention or protocol.

When asked to give a verbal rating of the sensation of NMES from unbearable to very comfortable, 24 (63%) of the subjects rated it as very comfortable or comfortable with the rest of the subjects rating it as bearable. 36 (95%) of the subjects considered NMES an acceptable form of treatment. The median rating of pain on a scale of 0 to 100 at the start of the study was 16 (min=1, max=68) representing mild levels of pain on average with no one rating pain in the severe category. The median rating of pain at the end of the study was 7.5 (min=1, max=60), again with no one in the severe pain category. The rating of pain reduced by 6 on average (min change= - 46, max change = 21).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Descriptive statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stocking size</td>
<td>n (%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>3</td>
<td>13 (34.2%)</td>
</tr>
<tr>
<td>4</td>
<td>18 (47.4%)</td>
</tr>
<tr>
<td>5</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>Mean calf diameter (SD)</td>
<td>37.3 cm (2.61)</td>
</tr>
<tr>
<td>Mean sub bandage pressure (SD)</td>
<td>47.3 mmHg (5.31)</td>
</tr>
<tr>
<td>Mean stimulation right (SD)</td>
<td>53.7% (13.49)</td>
</tr>
<tr>
<td>Mean stimulation left (SD)</td>
<td>54.3% (13.57)</td>
</tr>
</tbody>
</table>

Table 8-1: Summary of stocking size, calf diameter, sub bandage pressure and stimulation (n=38)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>HUT Protocol</th>
<th>Active Stand Protocol</th>
<th>P-value for Intervention</th>
<th>P-value for Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in systolic BP (SD)</td>
<td>-28.8 (12.62)(^a)</td>
<td>-21.1 (8.26)(^b)</td>
<td>-31.5 (16.49)(^a)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>-21.6 (8.90)(^b)</td>
<td>-32.2 (14.81)(^ab)</td>
<td>-26.9 (16.32)(^b)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean change in diastolic BP (SD)</td>
<td>-13.9 (10.51)</td>
<td>-11.8 (7.24)</td>
<td>-15.5 (10.23)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>-12.3 (7.26)</td>
<td>-13.2 (9.07)</td>
<td>-12.3 (13.20)</td>
<td>0.44</td>
</tr>
<tr>
<td>Median change in heart rate (IQR)</td>
<td>5.0 (7.75)</td>
<td>3.0 (6.00)</td>
<td>9.0 (10.00)</td>
<td>0.67</td>
</tr>
<tr>
<td></td>
<td>3.0 (7.00)</td>
<td>10.0 (13.00)</td>
<td>9.0 (8.00)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean Peak systolic velocity (SD)</td>
<td>7.1 (1.53)(^a)</td>
<td>6.7 (1.32)(^a)</td>
<td>22.2 (5.58)(^b)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>7.5 (1.68)(^a)</td>
<td>7.6 (2.31)(^a)</td>
<td>25.0 (5.62)(^b)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median venous blood flow (IQR)</td>
<td>65.0 (41.25)(^a)</td>
<td>32.5 (25.75)(^b)</td>
<td>172.5 (75.5)(^c)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>70.0 (27.0)(^c)</td>
<td>50.0 (42.0)(^c)</td>
<td>180.0 (53.75)(^c)</td>
<td>0.11</td>
</tr>
<tr>
<td>Median rating of symptoms (min, max)</td>
<td>7.0 (5.25)(^a)</td>
<td>6.0 (7.50)(^b)</td>
<td>5.0 (8.00)(^b)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>7.0 (7.75)(^a)</td>
<td>7.0 (3.25)(^b)</td>
<td>6.0 (4.00)(^b)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Table 8-2: Haemodynamic parameters and symptom evaluation by intervention and protocol (n=38)

\(^abc\) Subscripts relate to pairwise comparisons within each protocol where intervention is a statistically significant factor in repeated measures ANOVA. Different subscripts refer to statistically significant (p < 0.05) differences between the means of two groups.
Figure 8-3: Change in SBP by intervention for HUT
Figure 8-4: Change in SBP by intervention for Active Stand
Figure 8-5: Effect of intervention on SBP over time for HUT (nadir BP not included)
Figure 8-6: Effect of intervention on SBP over time for Active Stand (nadir BP not included)
8.4 Discussion

This study has demonstrated that alternate leg calf muscle NMES is as effective as ECS in attenuating SBP reductions in older community dwelling subjects with OH during active and passive orthostatic challenges. NMES has been shown to have a positive effect on symptoms and is tolerable. This is the first study to our knowledge to demonstrate such findings comparing both interventions in an older group with OH. NMES-induced contraction of the calf muscles in healthy older subjects with OH appears to have similar haemodynamic effects to those seen with SCI. In those with SCI, NMES increases CO and SV, effects that are attributable to increased venous return to the right atrium (Davis et al. 1990; Raymond et al. 1999; Faghri and Yount 2002; Chi et al. 2008).

In the current study, alternate leg calf muscle NMES resulted in significant increases in venous peak systolic velocities and flow volume in comparison to control and ECS interventions reflecting local effects of stimulation which is consistent with earlier studies of those with chronic venous insufficiency (Lyons et al. 2002; Clarke Moloney et al. 2006). The effect of ECS on attenuating SBP reductions in our study is consistent with previous studies confirming their potential benefit in this group by reducing venous pooling in the lower limbs (Podoleanu et al. 2006; Privett et al. 2010). Symptoms were significantly improved in both NMES and ECS interventions over both protocols in comparison to control. When blood pressure (BP) falls upon standing, compensatory CA may maintain cerebral perfusion, minimising symptoms. Cerebral blood flow (CBF) is relatively independent of sympathetic influences except during very rapid changes and extremes of blood pressure (Hamner et al. 2010). Due to the effect on systemic BP, it appears both NMES and ECS may prevent significant CBF fluctuations resulting in fewer symptoms, however this requires further study potentially incorporating objective measures of CA such as trans-cranial doppler.

The VAS scores and questionnaire employed in this study were used to assess subject comfort. In this study, alternate leg calf muscle NMES has been demonstrated to be tolerable with the majority of participants describing the sensation either very comfortable or comfortable. On completion of the protocol,
there were no significant increases in discomfort or pain ratings. Almost all would consider NMES an acceptable form of therapy. VAS scores did not increase indicating perceived discomfort which is in keeping with earlier studies of healthy subjects and patients post orthopaedic hip surgery which incorporated longer study protocols (Broderick et al. 2010, 2011).

There are several strengths to this study. Both active and passive orthostatic challenges were used. With active standing, as opposed to passive standing, the body compresses and releases pressure on the veins of the lower limbs, forcing blood return to the heart, a process which is often called the “skeletal muscle pump” (Griffin et al. 2010). In addition, active standing activates a series of responses in the body that help to minimize blood pooling in the lower limbs, such as increases in abdominal pressure, decreases in vagal tone, and increases in cardiac and vascular sympathetic activity. This physiological difference can lead to marked differences in the hemodynamic responses of patients undergoing a passive tilt when compared to an active stand (Smith et al. 1994). In this study, there was a significantly greater reduction in SBP across all three interventions in the active stand protocol in comparison to the HUT. Without the aid of the skeletal muscle pump, venous return to the heart can decrease over time. Increased micro-vascular filtration of plasma into interstitial space on assumption of upright posture also contributes to decreased venous return by causing decreased blood volume, but, while it has been shown to occur in both tilt and active stand, the differences between the two tests have not been elucidated (Singer et al. 2012). Our results for the haemodynamic effect of NMES and ECS are consistent over both protocols. The inclusion of objective measurements of venous blood flow response to each intervention and compression strength of ECS enhance the applicability of our results. This represents the first study to report such findings in subjects undergoing active and passive orthostatic challenges.

This study has several limitations. Firstly, the population studied were a healthy older cohort of community dwelling subjects with OH. This may not be representative of an older, frailer, population with higher comorbidity who may commonly present with symptomatic OH. Over half of the subjects included in this study were overweight. Excessive subcutaneous fat thickness has been found to be
an important limiting factor in the conduction of current from the skin to the target neurons, due to its electrical resistivity and low blood flow resulting in less efficient muscle contraction (Lyons et al. 2004). In contrast to this, NMES usage in a potentially frailer group with less subcutaneous fat tissue may be complicated by lower tolerance levels and the need for reduced stimulation intensity which warrants further consideration. Secondly, the study design incorporated short duration interventions of only three minutes each following orthostatic challenge. The longer term effects of NMES on hemodynamic parameters, symptoms and tolerability in this group are unclear.

8.5 Conclusion

In summary, the present study represents a controlled investigation of the effect of NMES and ECS on hemodynamic parameters, symptoms and tolerability in an older community dwelling cohort of individuals with OH using both active and passive orthostatic challenges. The results support the hypothesis that NMES is effective in maintaining SBP, DBP, and HR during HUT and AS manoeuvres. These findings suggest that NMES may be used effectively to attenuate BP reductions in this group and is tolerable resulting in an improvement in symptoms. Further research is recommended to establish the longer-term clinical efficacy of NMES in older subjects with OH.
Chapter 9
Discussion and Conclusion
9.1 General Discussion

9.1.1. Introduction

The primary aim of this thesis was to investigate the potential benefit of neuromuscular electrical stimulation (NMES) as a non-pharmacological treatment strategy for orthostatic hypotension (OH) in older, community dwelling adults. The studies included in this thesis are the first to evaluate the effects of NMES on OH in this important population group and provide an original contribution to the current literature.

The review of the literature relevant to OH presented in chapter two highlights the clinical relevance of OH (Angelousi et al. 2014) and current limitations in high quality evidence regarding therapeutic efficacy (Logan and Witham 2012). Chapter three summarised the methodology of NMES and clinical applications including its demonstrated efficacy in patients with autonomic dysfunction following spinal cord injury (SCI) (Sampson et al. 2000; Faghri et al. 2001; Faghri and Yount 2002). Pathophysiological considerations in those with OH, and the potential role calf muscle pump augmentation (Madhavan et al. 2005, 2008) to facilitate venous return provide the hypothetical basis for the clinical research studies included in this thesis.

9.1.2. Discussion of Results

The first study presented in chapter five evaluated current specialist physician prescribing patterns of elastic compression stockings (ECS), which are commonly prescribed for patients with orthostatic intolerance (OI) (Maggi and Brignole 2007), and issues related to compliance reported by older patients. Physicians correctly identified the main reasons for non-compliance, however there were significant differences between patient compliance and physician predictions. In the patient survey it was found that although prescribed frequently, the use ECS in older patients with OH is often limited by issues related to practicality and perceived neutral effect on symptoms. The results of this study contrast with previous studies investigating compliance levels in patients following lower limb thromboembolism (Kahn et al. 2003; Roche-Nagle et al. 2010), however a younger study group with
less comorbidity may in some way explain this difference. The results presented are the first to evaluate issues relating to patient compliance in those with OH who use ECS and provides useful information for physicians who may frequently similar patients.

The feasibility study presented in chapter six demonstrated that calf muscle NMES may be useful in attenuating blood pressure (BP) reductions in older healthy subjects with OH during passive orthostatic stress (head-up tilting), using a randomised crossover study design. The alternate NMES setting resulted in the smallest systolic blood pressure (SBP) drop in comparison to simultaneous leg stimulation. This is the first study to evaluate the effects of both NMES settings on haemodynamic effects during head-up tilting. The possible reasons for larger reductions in orthostatic blood pressure (BP) in the simultaneous leg NMES setting group remain unclear, however may be comparable to the simultaneous activation of lower limb muscle pumps seen when standing up from a sitting position (Rossberg and Penaz 1988; Convertino et al. 1998; Krediet et al. 2007), which results in lower initial BP due to a reduction in total peripheral resistance. Similar effects on cardiac output (CO) and stroke volume (SV) in response to alternate leg NMES were seen as in previous studies investigating its effects in patients with SCI (Raymond et al. 1999; Faghri and Yount 2002). The haemodynamic effects of NMES in an otherwise healthy, older population appear to be similar to those with SCI who exhibit low levels of efferent sympathetic nervous activity resulting in the loss of reflex vasoconstriction following orthostasis. This study identified several issues that necessitated protocol modifications for the design of the subsequent studies included in this thesis. These included the recording of objective measurements of symptoms following orthostasis, tolerability of NMES and assessment of popliteal venous blood flow responses to NMES.

In chapter seven, the effects of both alternate and simultaneous calf muscle stimulation were investigated in young, healthy participants during head-up tilting. Similar to the study in chapter six, alternate leg NMES resulted in the most favourable haemodynamic responses. Both NMES settings were found to tolerable although the majority preferred the alternate setting when given a choice. Popliteal
venous blood flow measurements were significantly increased in both NMES interventions in comparison to control, which is similar to earlier studies (Clarke Moloney et al. 2006; Corley et al. 2009; Broderick et al. 2013). As would be expected in a young, healthy study population, symptoms following orthostasis were relatively infrequent, however this method of symptom assessment using a visual analogue scale during the protocol was found to be a practical method of assessment. Following this study, in view of the favourable haemodynamic effects and subject preference demonstrated, alternate leg calf muscle NMES was chosen for use in the final study in chapter eight.

This study in chapter eight represents a controlled investigation of the effect of alternate leg calf muscle NMES and ECS on haemodynamic parameters, symptoms and tolerability in a cohort of older, community dwelling individuals with OH using both active and passive orthostatic challenges. The results demonstrated significant improvements in SBP, diastolic blood pressure (DBP), and heart rate (HR) in both alternate leg calf muscle NMES and thigh length ECS interventions during head-up tilt and active stand protocols in comparison to control. There was no significant difference found between NMES and ECS over both protocols. The results of this study support the hypothesis that alternate leg calf muscle NMES is as effective as ECS in preventing BP reductions in this subject group, and represents the first such study to date to report these findings.

9.2. Limitations

The studies included in this thesis have several limitations. Previous studies investigating the effects of surface NMES in patients with SCI have generally incorporated stimulation protocols at thigh level (Faghri et al. 1992, 2001; Sampson et al. 2000; Faghri and Yount 2002). As discussed earlier, improvements in orthostatic BP by applying counter-pressure to the whole leg and/or abdominal segments have been demonstrated (Denq et al. 1997; Smit et al. 2004; Podoleanu et al. 2006; Platts et al. 2009; Stenger et al. 2010). Although calf muscle NMES has been found to attenuate BP reductions in the present studies, the effect of NMES at thigh level in older subjects with OH requires future study as this may potentially
result in higher increases in venous return in response to stimulation than that at calf muscle level.

The older population with OH studied in chapters six and eight were a cohort of community dwelling subjects recruited from an earlier cross sectional study of social and physiological well-being in Limerick city (Humphreys e & deBurca s 2008), with the majority of participants included in the overweight BMI category. The haemodynamic effects of calf muscle NMES in this group may not representative of more complex, frailer older patients with either symptomatic neurogenic or non-neurogenic OH who frequently present for medical assessment. The effect of calf muscle NMES on these patients during orthostasis who also may exhibit reduced skin adiposity remains undetermined and requires further study, as possibly reduced stimulation intensity may be necessary. The frequency of symptoms during orthostasis in chapter eight was also low indicating that the majority of participants had asymptomatic OH who may have more robust cerebral autoregulation. Again, this is most likely explained by the relatively healthy study population with minimal comorbidity, and raises the question as to whether NMES will reduce symptoms in a multi-morbid, symptomatic group.

Finally, the cross-over design of the studies in chapter six to eight may have resulted in carryover effects of each interventions which could have possibly influenced the results. The likelihood of this was reduced by ensuring haemodynamic stability during the defined rest period of each intervention, although some finomter traces had to be excluded due to poor quality and failure to establish reliable baseline recordings. In chapter eight, both protocols were performed under the same conditions on successive days in the majority of subjects to reduce the potential for variability of the results between protocols.
9.3. Future Directions

The effects of lower limb NMES on posture and balance during orthostasis will be an important area for future study in development of this technology as a clinical application for OH in older people. Future study should include specific emphasis on balance parameters including distance and direction travelled by Center of Force (CoF), variability in distance travelled by CoF, weight-bearing percentage (left/right, fore/rear foot) and pressure distribution profiles (Jancová 2008) during NMES stimulation. With this in mind, the stimulation profile could potentially be modified to minimise the impact of soleus muscle stimulation on patient balance by increasing the ramp time to 3-4 seconds, whilst still resulting in optimal haemodynamic responses during standing.

Surface NMES devices need to portable and ergonomically convenient for patient use, specifically in an older population with dexterity or visual impairments. Future development of the NMES system may comprise a plurality of bio-mechanical sensors and processor adapted to use signals from sensors to determine risk of syncope as a result of OH, with activation of the NMES device during orthostasis, prior to symptom onset. Patient activity could be monitored using a single, trunk mounted miniature kinematic sensor, based on methodology previously described (Najafi et al. 2003). This sensor can detect subject posture (sitting, lying, standing, walking) and postural transitions and may be interfaced with the NMES device (Mansfield and Lyons 2003). When the kinematic sensor detects a change to upright posture (sit-to-stand, lying to standing), it can be set up to trigger the stimulation of the calf muscles. For an initial proof of concept study, a wired sensor system could be employed, however, it would be envisaged that the final product would incorporate a wireless sensor system. There is scope to consider NMES device modifications to improve portability such as implantation in clothing or stockings or indeed the development of implantable NMES devices in the lower limbs.

Future studies could also include an assessment of the effectiveness of stimulation for managing OH in older people in the home. Patients may wear the stimulator and the integrated trunk-mounted kinematic sensor continuously over a prolonged period in the home environment. This system may automatically detect transitions from
sitting or lying to upright standing, and will apply NMES stimulation to the calf muscles when changing posture. The efficacy of the system could be measured by the following:

- System reliability - accuracy in detecting posture change and delivering NMES.
- Comfort and tolerability - how comfortable and easy the system is to use over a prolonged period.
- Prevention of OH symptoms - did stimulation of calf muscles reduce the frequency and severity of OH symptoms?

9.4. Final Conclusion

The findings of the studies included in this thesis suggest that NMES may be used effectively to attenuate BP reductions in older, community dwelling subjects with OH during active and passive orthostatic challenges. NMES is tolerable in this group and results in an improvement in symptoms. Further research is recommended to examine the potential effects of NMES on posture and balance, and to establish the longer-term clinical efficacy incorporating kinematic sensor based technology.
References:


Appendix A: Ethical Approval

16th December, 2010

Dr. Colin Quinn,
SpR Dept. of Medicine,
Division of Ageing and Therapeutics,
Mid-Western Regional Hospital,
Dooradoyle,
LIMERICK

Re: Protocol Title
Current prescribing patterns of elastic compression stockings in patients with orthostatic hypotension.

Dear Dr. Quinn,

Thank you for attending the Research Ethics Committee meeting on the 15th December, 2010 in connection with your study.

I wish to advise that the Committee has now approved your study. However, you should note that your study cannot commence until you also receive Risk Management approval. This approval will be issued to you shortly.

You are obliged to inform us as soon as your study is completed or if it terminates early for any reason.

I wish you every success in your study.

Yours sincerely,

Marie Hickey Dwyer,
Consultant Ophthalmic Surgeon,
Chairperson, Ethics Research Committee.
25th March, 2010

Dr. Colin Quinn,
Department of Medicine for the Elderly,
Mid-Western Regional Hospital,
DOONAGHORE,
LIMERICK

Re: Protocol Title
Determination of the potential benefit of electrical stimulation induced calf muscle pump activation for syncope prevention.

Dear Dr. Quinn,

Thank you for attending the Research Ethics Committee meeting on the 24th March, 2010 in connection with your study.

I wish to advise that the Committee has now approved your study subject to only patients not currently on medication for orthostatic hypotension are included in this study. However, you should note that your study cannot commence until you also receive Risk Management approval. This approval will be issued to you shortly.

You are obliged to inform us as soon as your study is completed or if it terminates early for any reason.

I wish you every success in your study.

Yours sincerely,

Marie Hickey Dwyer,
Consultant Ophthalmic Surgeon,
Chairperson, Ethics Research Committee.
Appendix B: Related Publications and Presentations

Publications


Presentations:


Poster presentation British Geriatrics Society Spring Meeting 2014


Poster presentation British Geriatrics Society Spring Meeting 2011
Poster presentation Irish Gerontological Society Meeting 2011
Age and Ageing
2014 Vol. 44 (2), pp. 339-342
Therapeutic use of compression stockings for orthostatic hypotension: an assessment of patient and physician perspectives and practices
Quinn, Colin, Deegan, Brian, Cooke, John, Carew, Sheila, Hannigan, Ailish, Dunne, Colum and Lyons, Declan
http://dx.doi.org/10.1093/ageing/afu162
Appendix C: Participant Information Sheets

Study Title

Prescribing patterns of elastic compression stockings in orthostatic hypotension.

Introduction

You are being invited to part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. If there is anything that you are not clear about, we will be happy to explain it to you.

Thank you for reading this.

Purpose of the study

Sometimes, when people stand up from a sitting or lying position their blood pressure drops suddenly. This can lead to the person feeling dizzy and can occasionally cause them to fall over leading to a risk of broken bones and other injuries. We refer to this drop as “Orthostatic Hypotension”. Recent work performed here in Limerick suggests that there is a certain group of patients who are particularly vulnerable to this condition.

Treatment options for this condition can involve using compression stockings and also taking medications. These stockings work by compressing the lower leg, preventing the inflow of blood. By doing this more blood should be available to the heart and brain reducing the possibility of dizziness or a fall. Medications can be useful to treat this condition although sometimes their value is limited by side effects.

The purpose of this study is to evaluate the current prescribing patterns and uses of compression stockings by patients. With this information we hope to determine if patients find compression stockings a practical treatment option. The results of this study may influence future prescription of compression stockings and may also encourage development of newer alternative treatment options for this condition.

The questionnaire will take approximately 10 minutes to complete. It consists of 4 questions. The majority of questions are in multiple choice format and ask you to select the most appropriate answer. However there is opportunity for you to write further comments should you wish to do so.

This will be an anonymous study and responses will not be examined on an individual basis. The results of the study will potentially be published in a medical journal but any individual information obtained in connection with the study will remain confidential and will not be disclosed.
To ensure security the returned questionnaires will be stored in a locked filing cabinet in a secured area and will be destroyed on data entry. Data will be stored electronically in a database on a secure server and access is restricted by password to the researchers.

Taking Part

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you decide not to take part you are still free to withdraw at any time and without giving a reason.

A decision to withdraw at any time, or a decision not to take part, will not affect your ongoing medical management in any way.

Current prescribing patterns of elastic compression stockings in patients with orthostatic hypotension

I have read and understand the attached information sheet for this study. Any questions I have in relation to the study have been answered to my satisfaction. I am aware that I do not have to take part in the study. I understand that by completing and returning the questionnaire and signed consent form below that I agree to participate in the project and consent to the publication of the results with the understanding that anonymity will be preserved.

Volunteer ________________________ Date ____________________
(Please Print)

Signature ________________________
Study Title

_Determination of the potential benefit of electrical stimulation induced calf muscle pump activation for syncope prevention_

Introduction

You are being invited to part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. If there is anything that you are not clear about, we will be happy to explain it to you.

Thank you for reading this.

Purpose of the Study

Sometimes, when people stand up from a seated or lying position, their blood pressure drops suddenly. This can lead to the person feeling dizzy and can occasionally cause them to fall over leading to a risk of broken bones and other injuries. We refer to this drop in blood pressure as “Orthostatic Hypotension”. Recent work performed here in Limerick suggests that there is a certain group of patients who are particularly vulnerable to this problem.

The goal of the current study is to examine the possible benefits of two treatment options. The first treatment is the use of compression stockings. These stockings work by compressing the lower leg, preventing the inflow of blood. By doing this more blood should be available to the heart and brain and reduce the possibility of dizziness or a fall.

The second treatment is the use of electrical stimulation. By stimulating the muscles in the lower leg we may be able to promote the return of blood to the heart and brain. This may again reduce the possibility of dizziness or falls.

By changing your body position (for example tilting you from lying flat to upright, or standing up from a chair) we can examine changes in the regulation of blood flow that occur before symptoms such as dizziness and lightheadedness. We will be able to compare changes in your body’s blood flow to the different treatments.

We hope this study will help us to develop a deeper understanding of the changes in blood pooling with compression and with electrical stimulation. This will help us to design new interventions for treating orthostatic hypotension.

Risks to the subject

There is a risk of fainting during tilt testing. Heart rate and blood pressure usually return to baseline levels very quickly once the person is returned to horizontal. People will be monitored until it is deemed safe for them to leave the lab.
The sensation of electrical stimulation is often described as similar to ‘pins and needles’ and some people find it irritable/unusual at first.

**Taking Part**

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you decide not to take part you are still free to withdraw at any time and without giving a reason.

A decision to withdraw at any time, or a decision not to take part, will not affect your ongoing medical management in any way.

**Exclusion Criteria**

Please make the investigators aware of any of the following exclusion criteria:

- Psychotropic medications
- Pharmacological treatment for orthostatic hypotension
  - Midodrine
  - Fludrocortisone
  - Droxidopa
- Recent (<6 months) Myocardial Infarction / Stroke
- Permanent Pacemaker/ICD
- Blood volume depletion
- Total knee replacement
- Peripheral vascular disease
- Significant Cardio-respiratory disease

**Procedure**

This study will be completed over two sessions per person. Each session will last approximately 1&1/2 hours. If you agree to be in this study, you will be asked to read and sign this consent form. After you sign the consent form, the following things will happen.

**Screening Procedures:** These will already have been complete as part of your participation in the research to date

**Abstain from food:** You will be required to abstain from food for 4 hours prior to commencement of the study.

**Instrumentation:** During each of the study sessions, you will be required to wear the following monitoring devices:

- Electrocardiogram – Three sticky electrodes will be pasted to your chest to allow us to measure the electrical activity in your heart.
- Non-invasive Blood Pressure – A small cuff will be placed your finger that will inflate throughout the study to allow us to measure your blood pressure. We will also place a cuff around your upper arm, like the cuff your doctor uses to measure your blood pressure, which will inflate occasionally.
Head Up Tilt:
- You will lie flat on a tilt table
- After 5 minutes of resting, you will be tilted upright to 70°. This feels similar to standing.
- After 3 minutes recording, you will be returned to the horizontal position
- The test will be stopped immediately if you report symptoms such as dizziness, light-headedness or nausea as described above.

Electrical Stimulation Head Up Tilt:
- Electrodes will be applied to your legs (2 electrodes per leg).
- Leg strength will be measured using a hand held device which you push your foot against.
- The level of stimulation will be increased to a level that is comfortable but generates a strong muscle contraction, again measured using the hand held device.
- Stimulation will be applied to both legs alternately.
- Head-Up Tilt will be repeated as previously described.

Sit-to-stand test:
- You be seated in a chair for 5 minutes
- After 5 minutes of resting, you will stand up.
- After 1 minute of recording, you will sit back down in the chair
- The test will be stopped immediately if you report symptoms such as dizziness, light-headedness or nausea as described above.

Electrical Stimulation sit-to-stand:
- Electrodes will be applied to your legs (2 electrodes per leg).
- Leg strength will be measured using a hand held device which you push your foot against.
- The level of stimulation will be increased to a level that is comfortable but generates a strong muscle contraction, again measured using the hand held device.
- Stimulation will be applied to both legs alternately.
- Sit-to-stand will be repeated as previously described.
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.
Thank you for your participation.
I have read and understand the attached information sheet for this study. Any questions I have in
relation to the study have been answered to my satisfaction. I am aware that I do not have to take part
in the study and that I can withdraw at any stage without explaining my reasons for doing so. I
understand that withdrawing from the study will not affect my present or future medical treatment.

Volunteer ________________________ Date ____________________
(Please Print)

Signature ________________________

Witness/Guardian ____________________ Date ____________________
(Please Print)

Signature ________________________

Investigator _______________________ Date ____________________
(Please Print)

Signature ________________________