CARDIOVASCULAR RESPONSE TO FUNCTIONAL ELECTRICAL STIMULATION AND PASSIVE STEPPING TO IMPROVE ORTHOSTATIC TOLERANCE

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A thesis submitted in conformity with the requirements for the degree of Masters of Applied Science and Engineering

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ABSTRACT

Title: Cardiovascular Response to Functional Electrical Stimulation and Passive Stepping to Improve Orthostatic Tolerance

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Abstract: Functional electrical stimulation has been used to attenuate the haemodynamic response to orthostatic stress in patients with autonomic disorders. It is believed that involuntary skeletal muscle pump activation increases the venous return and thereby mediates the effects of orthostatic stress. This theory has not been studied extensively in healthy individuals and thus the haemodynamic effect of involuntary stimulation is not well characterized. This study investigated the hemodynamic response from upright tilt during involuntary skeletal muscle pump activity using functional electrical stimulation (FES) and passive mobilization movement. The subjects experience orthostatic stress for 15 minute durations during which blood pressure, heart rate, and blood volume changes were recorded. During head-up tilt, application of FES to the lower limb muscles while the legs were not moving (isometric FES) was found to significantly increase heart rate, whereas the combination of FES with passive mobilization movements of the lower limb (dynamic FES) increased blood flow and cardiac output. Since dynamic FES may be better able to improve orthostatic tolerance, this modality should be further investigated as a potential therapy to prevent orthostatic intolerance.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Orthostatic hypotension (OH) is a clinical condition defined as a sudden drop in blood pressure upon upright postural change. (1) In the first three to five minutes following head-up tilt (HUT), up to one litre of blood can pool in the lower extremities, resulting in a decrease in venous return and a subsequent reduction in cardiac output by up to 20%. (2, 3) This condition is common in cases of traumatic brain injury (4) or spinal cord injury (SCI). (2, 5) These individuals will experience venous pooling resulting from sympathetic nervous system dysfunction. In fact, 74% of individuals with SCI experience episodes of dizziness, lightheadedness (pre-syncope) or loss of consciousness (syncope) upon postural change. (6) These symptoms may impair the individual during the acute phase of SCI, and in some cases may persist for years. (7) Furthermore, OH interferes with the patient's rehabilitation, which is necessary to promote neural recovery, prevent muscle atrophy, mitigate osteoporosis, and to maximize clinical outcomes. (8) Therefore, OH delays rehabilitation, prolongs bed rest and promotes further cardiovascular deconditioning.

Current OH treatment modalities include the use of elastic compression stockings, abdominal binders, pharmacological measures, and progressive mobilization exercises from supine to vertical posture. (9) However, there are many individuals with SCI for whom these treatments are ineffective. (10) Thus, new therapies are needed to improve orthostatic tolerance. One such approach is the use of functional electrical stimulation (FES) to improve venous return. (2, 11) We have found that FES can reproduce functional movements, such as walking (12) and grasping. (13) In addition, several recent studies have investigated the use of FES to improve venous return in healthy (14-16) and SCI populations. (15-18) Alternatively, venous return can also be enhanced by exercise, since lengthening and shortening of muscle fibres will contribute to muscle pump activation. (19) Thus, another approach for improving orthostatic tolerance in individuals with SCI is to create locomotor movements, such as stepping. Based on the rat model, the literature suggests locomotion is more effective for increasing venous return when compared to isometric FES. (19) To date, one study has examined the effects of passive leg movements on improving orthostatic tolerance in humans, (20) showing that passive mobilization therapy performed on the Erigo dynamic tilt table was effective in improving OH during tilt. However there is no information comparing the effectiveness of isometric FES to passive mobilization. In addition to isometric FES and passive mobilization, the combination of the two modalities, which consequently produces a dynamic FES modality, is an untested model which may be effective in improving venous return during head up tilt. Thus, the purpose of this study was to investigate the effect of isometric FES, passive mobilization, and dynamic FES on improving orthostatic tolerance in healthy subjects.

BACKGROUND

Autonomic Nervous System

The autonomic nervous system controls blood pressure and heart rate by the manipulation of sympathetic and parasympathetic nervous systems.

Sympathetic activity is excitatory, and prepares the body for a "fight or flight" response. The sympathetic axons exit the ventral roots of the spinal cord, and synapse with postganglionic synaptic neurons before innervating tissues and organs under sympathetic control. Innervation of the sympathetic system will strengthen myocardial contractions and increase heart rate and peripheral vascular resistance thereby elevating blood pressure.

Parasympathetic activity is generally inhibitory, and activity will result in inhibition of sympathetic system. Visceral parasympathetic control is regulated though the vagus nerve which exits from the brain at the brainstem going on to innervate the tissues and organs under parasympathetic control. The parasympathetic response leads to a decrease in myocardial contractions and a lowering of hear rate thereby reducing blood pressure

The extent of autonomic control is dramatic. Activation of the sympathetic system can double heart rate in 5 seconds, and blood pressure in 15 seconds. Likewise, parasympathetic activation can decrease blood pressure and induce syncope within 4 seconds of activity. (21)

Heart and Circulation Function

The heart is comprised of two separate "hearts". The right heart pumps blood to the pulmonary circulation and the left heart pumps blood to the systemic circulation. Both left and right hearts have two chambers, the atrium and then ventricle. The atrium functions as a primer, pumping blood into the right ventricle by means of the tricuspid valve or left ventricle by the mitral valve. The ventricle serves to pump blood into the pulmonary circulation by the pulmonary valve or into the systemic circulation by the aortic valve. The pumping activity, known as the cardiac cycle, occurs continuously averaging 72 beats per minute in a healthy individual. The cardiac cycle has two phases, diastole and systole. During diastole, the atriums prime both ventricles by filling each with blood. During systole, the ventricles contract pumping blood to the pulmonary and systemic circulations. (21)

Circulation is divided into systemic and pulmonary circulatory pathways. The pulmonary circulation provides blood flow to the lungs, whereas the systemic circulation provides blood flow to the rest of the body. The arteries are responsible for transport of oxygenated blood under high pressures to tissues. The veins on the other hand transport deoxygenated blood from the tissues back to the heart. (21)

Since the pumping of the heart is pulsatile, the arterial pressure will fluctuate with a systolic pressure of 120 mm Hg and a diastolic pressure of 80 mm Hg. As blood flows through the systemic circulation, blood pressure will reach 0 mm Hg at the vena cava during which point the blood will empty into the right atrium. Three principles guide circulation: blood flow to each tissue is precisely controlled by the tissue's need, total blood flow through the heart is controlled by the sum of all local tissue flows, and arterial pressure is independent of either local blood flow or total blood flow effects. (21)

Cardiac output (CO) is the most critical circulatory information. It is defined as the quantity of blood pumped by the heart each minute. In able bodied individuals, CO is equivalent to venous return (VR), which is the amount of blood flowing from the veins into the right atrium each minute. During rest, upright CO is approximately 5.6 L/min in able bodied individuals, but with the onset of exercise CO will increase at a rate based on the level of activity. (21)

Regulation of Hemodynamics under Orthostatic Stress

The veins are highly distensible and contains 64 percent of the body's blood volume. (21) Due to the increased distensibility, venous blood will pool upon immediate orthostatic stress. Within 10 seconds of quiet standing, the majority of the venous pooling will have occurred, and within 5 minutes, a steady state pooling level will be reached. In this manner, up to 1 L of thoracic blood can be transferred below the diaphragm. After 10 minutes of orthostatic stress, 10 - 20 percent of the blood volume will be lost from the systemic circulation as increased capillary pressure causes fluid to leak into the tissue space. Consequently, VR is reduced which will reduce CO by 20 percent. (2, 22)

There are three systems important for the regulation of CO. Neural control regulates the initial response to orthostatic stress, humoral control regulates prolonged stress, and specific vascular regions which can be used to mediate both acute and prolonged response.

Neural control involves the baroreceptors, located in the aortic arch and carotid sinus, and cardiopulmonary receptors, located in the heart and lungs. The baroreceoptors are believed to be the most important regulator during upright stance. During tilt, baroreceptors will sense the fall in blood pressure, thereby eliciting a strong sympathetic discharge which attenuates the decreasing blood pressure. During prolonged orthostatic stress, the renin-angiotensin vasoconstrictor mechanism can be effective for increasing blood pressure. When arterial pressure falls, renin is synthesized in the kidneys that will activate angiotensin II in the lungs, which causes vasoconstriction leading to increased arterial pressure. (2)

Specific vascular regions exist in the body which can mediate decreasing arterial pressure. The cutaneous vasculature is richly innervated and is principle for sympathetic thermoregulatory control. The splanchnic region contains 25 percent of the total blood volume and is a major site for autonomic regulation due to orthostatic stress. Most important however is the activation of the skeletal muscle pump, which occurs by muscle contracture that causes vasoconstriction of the venous and arteriole beds, thereby propelling blood toward the heart. Studies have investigated the use of muscle pump exercises in reducing orthostatic pooling. One such study found that slight postural sway during standing was enough to reduce venous pooling. Another found that repeated contractions of calf and thigh muscles could reduce venous ankle pressure from 100 to 40 mm Hg, thereby increasing venous return. Although quantitative data of skeletal muscle activity is limited, it is however believed to have major importance in counteracting orthostatic stress. (2)

Blood Pressure & Heart Rate Measurement

The most accurate method of non invasive blood pressure monitoring is by sphygmomanometer cuff. This technique occludes the artery by use of a pressure cuff. When the cuff pressure is reduced, systolic and diastolic pressures can be detected. The error from non invasive cuff method when compared to direct invasive methods varies by 2 to 8 mm Hg depending on measurement technique and experience. This protocol has been automated using pressure sensors to record systolic and diastolic pressures and a servo controlled system to regulate cuff pressure. In addition to blood pressure monitoring, the sphygmomanometer cuff technique can be used to monitor heart rate since the arterial pressure pulses correspond to the beating of the heart. In automated systems, heart rate is automatically calculated along with blood pressures. In general this technique is very susceptible to artifacts caused by limb movement or muscle tension. (23)

Functional Electrical Stimulation

Functional electrical stimulation (FES) elicits motor neuron activity resulting in muscle contractions. The method of stimulation can very, as some FES devices use surface electrodes while others use implanted electrodes. To produce muscle contraction or physical movement, the device delivers current at variable amplitudes, frequencies and pulse widths. Though FES has been used for SCI research since the 1960s, the application of FES in the management of orthostatic stress is much more recent. (24)

METHODS

Participants

A convenience sample of ten healthy male subjects who reported no history of cardiovascular, endocrine, or neuromuscular disease participated in this study. Subjects were non-smokers and were not taking any type of medication. Subjects were instructed to avoid alcohol and caffeine for 24 hours, fast for 8 hours, and drink nothing 2 hours prior to the study. All tests were conducted between 1600 and 2200 hours, in a quiet room with an ambient temperature between 19-21°C. Approval was acquired from the local university ethics committee and all subjects provided written informed consent.

Protocol

This study employed a randomized cross-over design, wherein each subject participated in a single session consisting of four 70° head-up tilt conditions. Previous studies have shown that syncope is most likely to occur at angles above 60°. (25)

A) Control (HUT)

B) Isometric FES (IFES)

C) Passive Mobilization (STEP)

D) Dynamic FES (DFES)

Subjects were positioned supine on an Erigo dynamic tilt table (Erigo. Hocoma AG, Switzerland) and secured using torso and shoulder harnesses (Figure 1). Subjects' thighs were attached to robotic actuators with soft straps and feet were loosely secured to the foot plates via a strap placed over the metatarsal joints so that the heels could separate from the foot plates to allow for non-obstructed venous pooling when upright. An automated blood pressure cuff and pulse monitor (HEM-637. Omron Healthcare, USA) was placed over

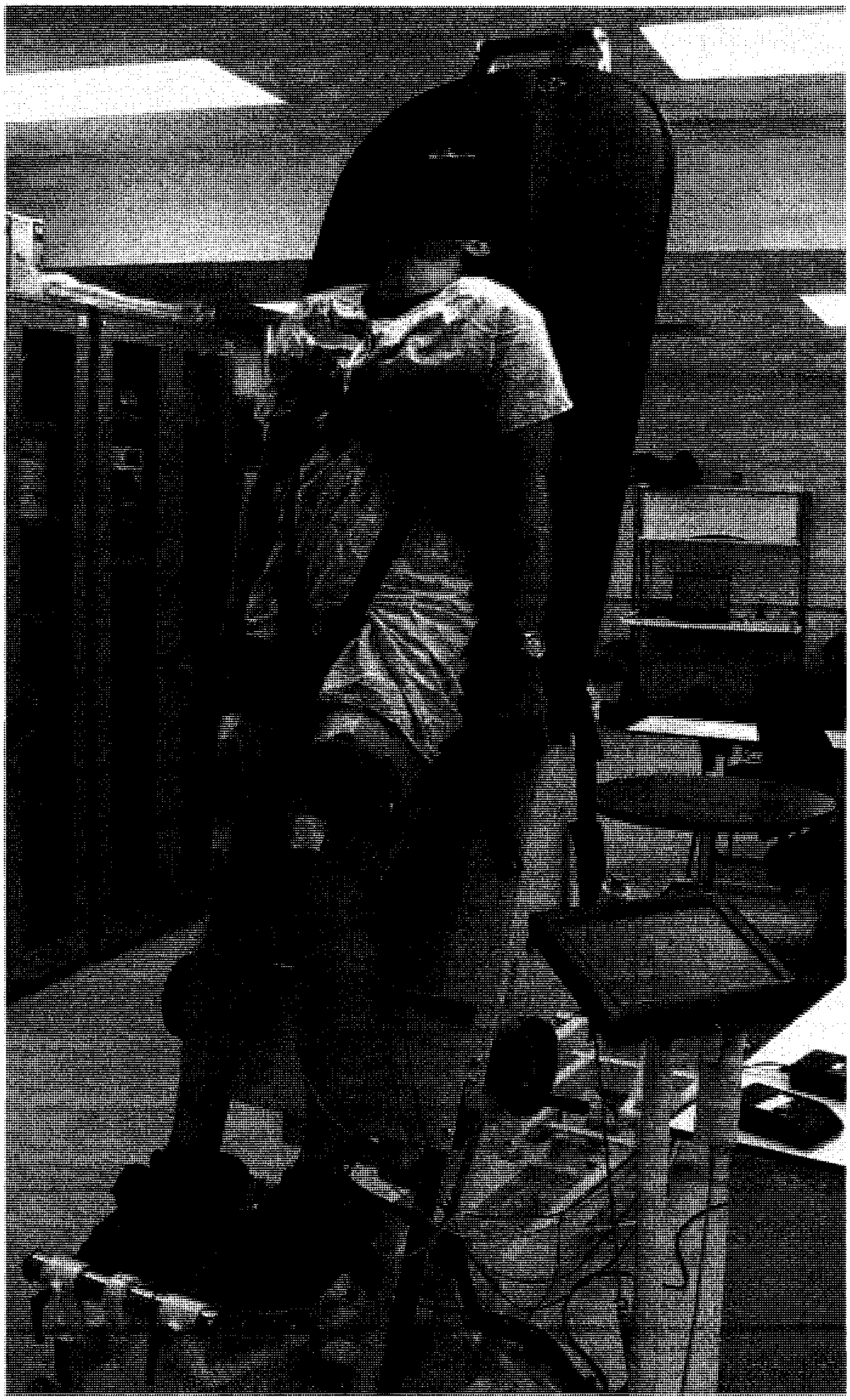

Figure 1: The experimental setup. Subjects were secured onto the tilt-stepper with torso and shoulder harnesses. Actuators attached to the thighs perform passive movements. FES was applied to the left and right quadriceps, hamstring and gastrocnemius muscles.

the left brachial artery, which remained at heart level for the duration of the experiment. The cross-sectional area of the inferior vena cava (IVC_{CSA}) was measured by by Doppler ultrasound (Acuson Aspen, Aspen Corporation, USA) imaging (Figure 2). The probe was positioned 1.5 cm below the diaphragm in the hepatic segment of the IVC. (26-29) Participants were scanned in the supine and upright positions prior to the start of the experiment in order to accommodate for vessel movement resulting from postural change.

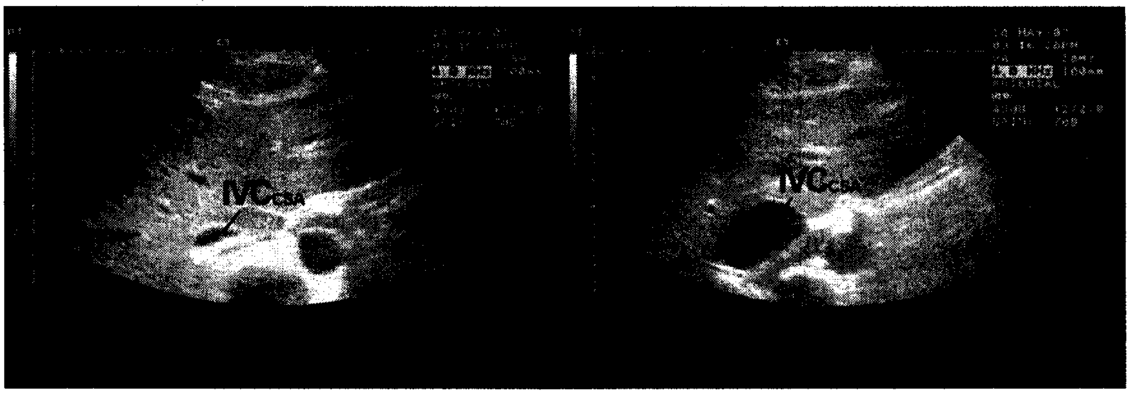

Figure 2. Representative changes in IVC_{CSA} from same subject. (A) IVC at 15 minutes of rest condition. (B) IVC at 15 minutes of dynamic FES condition.

To obtain baseline hemodynamic measurements, all subjects rested in the supine position for 20 minutes prior to the start of the experiment, although 5 minutes is sufficient based on the literature. (30) To control respiration, subjects were instructed to breathe in synchrony with a metronome at a rate of 15 breaths per minute. Subjects experienced randomized head-up tilt conditions for 15 minute periods. Blood pressure, heart rate and IVC_{CSA} measurements were recorded at baseline immediately prior to each tilt and at the onset, 5, 10 and 15 minute interval of tilt. Elevation to 70° from the supine position took approximately 25 seconds. Following each tilt condition, subjects were returned to the supine position for 10 minutes to re-establish steady-state hemodynamic conditions. Baseline hemodynamic stability was verified in each case.

Apparatus and setup

Two programmable 4-channel neuromuscular electrical stimulators (Compex Motion, Compex SA, Switzerland) were used to deliver transcutaneous FES to the left and right hamstring, gastrocnemius, and quadriceps muscle group. We choose not to stimulate the tibialis anterior muscle, since it did not significantly increase venous return (data not published). The stimulators produced a biphasic waveform with 30 Hz frequency, 300 μs pulse duration, at the maximum tolerable stimulation amplitude (amplitude varied from 17 – 40 mA between subjects) for 15 minutes. For each muscle, the motor threshold was determined by gradually increasing the stimulation amplitude until palpable contraction occurred. The stimulation sequence, consisting of 24 isometric FES cycles per minute, contracted the left gastrocnemius and quadriceps simultaneously with the right hamstring for one half of the cycle, and the right gastrocnemius and quadriceps simultaneously with the left hamstring during the second half of the cycle. Palpable strong muscle contractions and slight movement of the subject's legs were evident for all individuals.

An Erigo dynamic tilt table (Erigo, Hocoma AG, Switzerland) was used to induce passive mobilization through the use of robotic actuators. The tilt-table (Figure 1) induces a stepping motion by alternating hip and knee flexion and extension as well as a small range of ankle dorsiflexion, in a sequence that imitates gait. (20) When both Erigo and FES were used in combination FES systems and the tilt-table stepping were synchronized at 24 steps per minute,, such that left hip and knee extension coincided with left gastrocnemius and quadriceps stimulation.

Intravascular circulation blood flow was estimated by Doppler ultrasound (Acuson Aspen, Acuson Corporation, USA) imaging of the IVC_{CSA} in sequential B-mode with a 5

MHz probe. The probe was fixed in place with a custom made holder, which prevented rotational and translational movements of the probe head throughout the experiment.

Due to the distensibilty of the IVC and the non-pulsatile conditions which resulted in constant velocity flow profiles, the blood flow returning from the lower limbs correlated closely with the change IVC_{CSA}. (26-29) Therefore, one-minute recordings of the IVC_{CSA} were imaged for each interval period and frame-by-frame analysis was performed using image processing software (ImageJ, NIH, USA) to calculate the IVC_{CSA}. In accordance with pervious studies, the IVC_{CSA} was calculated as the mean maximal cross-sectional areas for each one-minute recording period. (26)

Statistical Analysis

All values of heart rate, blood pressure, and IVC_{CSA} were normalized with respect to the values measured at the end of each supine rest period immediately before tilt. A three-way repeated measures ANOVA was used to test the independent effect of FES, passive mobilization and tilting duration on heart rate, blood pressure, and IVC_{CSA}. Alpha was set at 0.05 for all procedures. Where significant within-subject effects were found with the ANOVA, Dunnett's post-hoc test was used to compare mean values of each condition to the HUT condition. This test was used to identify the conditions that are significantly different from the control group. (31) Statistical significance was assumed when p-values were less than 0.05. All data are reported as means ± SE.

RESULTS

Anthropometric data from all subjects are presented in Table 1. One subject experienced pre-syncope during the 15 minutes HUT condition. No subjects experienced any symptoms of pre-syncope or syncope during IFES, STEP or DFES conditions.

Subject	Age (yrs)	Height (cm)	Weight (Kg)	Body Mass Index
1	21	182	82	24.8
2	23	177	63	20.1
3	23	182	80	24.2
4	22	188	88	24.9
5	23	175	65	21.2
6	30	183	82	24.5
7	21	186	86	24.9
8	27	178	75	23.7
9	31	169	64	22.4
10	19	193	79	21.2
Mean	**24**	**181.3**	**76.4**	**23.2**
SD	**4**	**6.9**	**9.3**	**1.8**

Table 1: Summary of Subject Data

Changes in normalized IVC_{CSA} for each condition over 15 minutes of HUT are shown in Figure 3. A progressive decline in the IVC_{CSA} from rest was observed for both the HUT (0.80±0.10) and IFES (0.80±0.07) conditions. For the first 10 minutes of tilt, STEP (1.13±0.15) and DFES (1.08±0.08) conditions were able to increase the IVC_{CSA} from rest. However, STEP (1.02±0.12) was unable to maintain the increased IVC_{CSA} after 15 minutes of tilt, whereas DFES (1.15±0.07) did manage. By comparing each condition to that of HUT, a 44% ($p = 0.04$) increase in IVC_{CSA} was observed for the DFES condition after the 15 minute interval.

Normalized heart rate was elevated for each condition over the 15 minute tilt duration (Figure 4). During HUT, heart rate increased gradually for the first 10 minutes (1.35±0.05) but reverted to initial tilt values (1.30±0.03) over the last 5 minutes of tilting. Similarly, DFES produced a gradual increase in heart rate, with a more pronounced peak occurring at 5 minutes post-tilt (1.36±0.06). IFES produced an abrupt increase in heart rate at tilt onset (1.44±0.07) which was sustained for the duration of tilt (1.45± 0.04). STEP elevated and sustained the heart rate through the duration of the tilt. In comparing each condition to HUT, a 12% (p = 0.02) increase in heart rate was observed during the IFES condition after 15 minutes.

There was no significant change in the normalized systolic blood pressure (SBP) and diastolic blood pressure (DBP) values when compared to the HUT condition. SBP increased slightly over the tilting duration under HUT (1.09±0.02), IFES (1.09±0.02), and DFES (1.09±0.01) conditions. For STEP, SBP (Figure 5) remained consistent (1.04±0.02) after 15 minutes. DBP increased during the first 5 minutes of HUT (1.20±0.04), and then remained constant for the remainder of the condition (Figure 6). DBP decreased during gradually during IFES. Both STEP and DFES produced an initial increase in DBP, which was attenuated after 5 minutes of tilt.

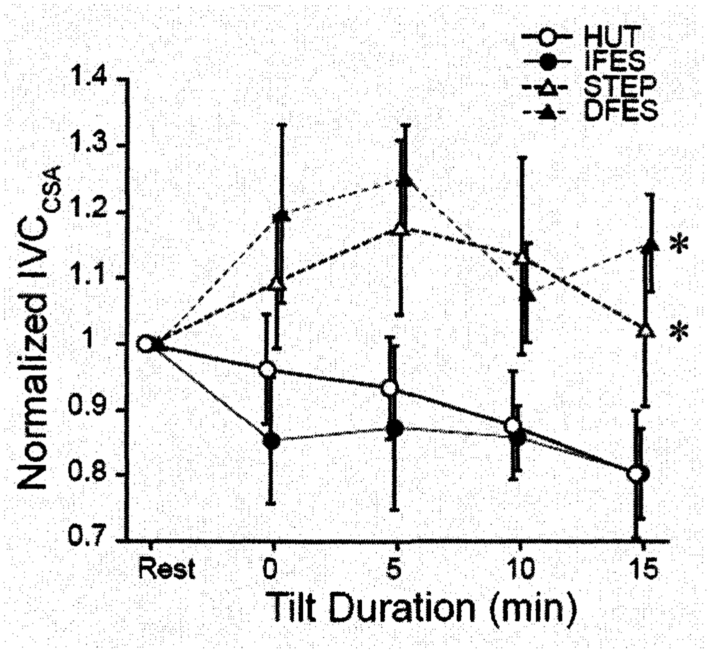

Figure 3: Inferior vena cava cross-sectional area values normalized to supine baseline measurements for each condition over 15 minutes of HUT. Passive stepping ($p < 0.001$) and dynamic FES ($p = 0.007$) were found to exert significant effects on IVCcsa. * indicates $P < 0.05$ for the post-hoc test.

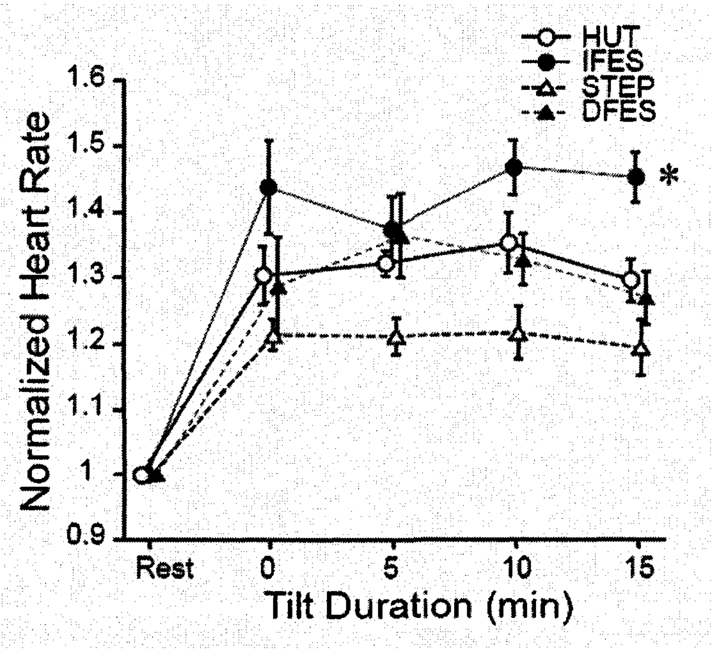

Figure 4: Heart rate values normalized to supine baseline measurements for each condition over 15 minutes of HUT. Isometric FES ($p = 0.002$) and passive Stepping ($p = 0.001$) were found to exert significant effects on heart rate. * indicates $P < 0.05$ for the post-hoc test.

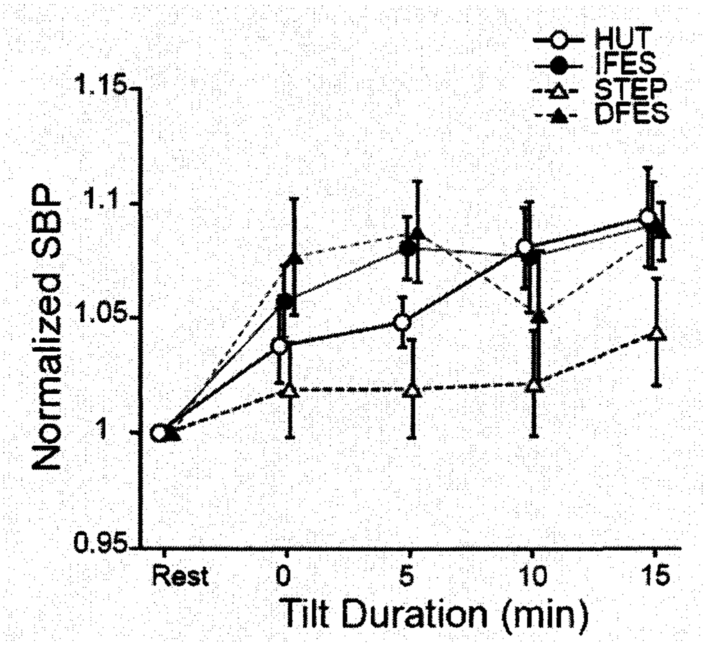

Figure 5: Systolic blood pressure values normalized to supine baseline measurements for each condition over 15 minutes of HUT. The ANOVA did not find any significant effects on systolic blood pressure.

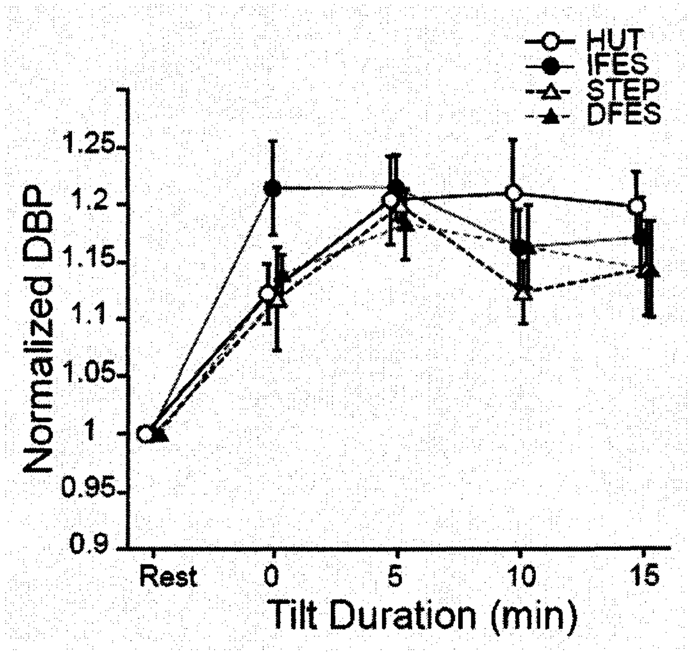

Figure 6: Diastolic blood pressure values normalized to supine baseline measurements for each condition over 15 minutes of HUT. The ANOVA did not find any significant effects on diastolic blood pressure.

DISCUSSION

This study compared the effects of isometric FES, passive movement and dynamic FES during orthostasis by monitoring the change in blood pressure, heart rate, and blood flow. Our results show that during orthostatic challenges, blood pressure was maintained, while heart rate increased and blood flow decreased. The application of isometric FES was able to increase the heart rate, but did not significantly affect blood flow. Passive mobilization did not produce significant effects. The application of dynamic FES was able to attenuate the decrease in blood flow during the head up tilt protocol. Therefore, dynamic FES has the greatest potential to increase the duration of orthostatic tolerance.

Blood Flow Response

During HUT, a 20% reduction in the size of the IVC_{CSA} was observed over 15 minutes. This is in accordance with healthy subject's response to orthostatic stress. (2) It is interesting to note that isometric FES conditions also resulted in a 20% reduction in mean IVC_{CSA}, whereas passive mobilization was maintained (2%) and dynamic FES increased mean IVC_{CSA} (15%).

The reduction in mean IVC_{CSA} during isometric FES is in accordance with a study that assessed muscle pump function on venous return in healthy and SCI subjects. (16) However, contrary to our findings, another study had demonstrated that isometric FES can minimize venous pooling after 30 minutes of quiet standing in healthy subjects. (14) The disparity between our results when compared to quiet standing suggests individuals may experience differing cardiovascular responses under HUT and quiet standing conditions. This is possible, since brief static contractions in the leg muscles during upright stance will trigger the exercise and baroreceptor reflexes, (32) thus resulting in an immediate increase in heart rate and thereby affecting blood flow. Furthermore, quiet standing was found to have a greater tendency to induce syncope when compared to HUT, (33) which suggests that autonomic function and cardiovascular response differ between tilt and standing situations. Compared to isometric FES, passive mobilization and dynamic FES were able to either maintain or increase the mean IVC_{CSA}, suggesting that these modalities are more effective for maintaining or improving circulatory hemodynamics under orthostatic conditions.

Heart Rate Response

Healthy subjects experiencing orthostatic conditions will compensate by increasing heart rate to maintain cardiac output. (3) This was found to be true in our study, as mean heart rate increased by 30% for HUT. The most significant increase in mean heart rate (45%) occurred during isometric FES. Heart rate also increased for passive mobilization (19%) and dynamic FES (27%) but these occurred at levels less than that of the control condition.

It is possible that the main effect accounting for the dramatic 45% increase in heart rate during isometric FES is a consequence of sympathetic activity rather than cardiovascular function. This would help explain how isometric FES and the control condition both resulted in a 20% reduction in IVC_{CSA}. In this case, the increased heart rate during isometric FES can be attributed to increased sympathetic activity caused by electrical stimulation. The heart rate response for dynamic FES should reflect isometric FES, but does not. This can be explained by parasympathetic activity resulting from an increase in blood flow and stroke volume thereby counteracting the FES-induced sympathetic activity. This parasympathetic activity can also be used to explain the slight 19% increase heart rate observed during passive mobilization.

Blood Pressure Response

The literature on healthy subjects reports little or no change in SBP, and a gradual increase in DBP when experiencing HUT. (35) Our study was able to validate this finding, as SBP increased slightly (7%) and DBP increased gradually (18%) over the duration of tilt. We did not find significant differences in the blood pressures from the control condition for isometric FES, passive mobilization or dynamic FES conditions. This suggests that the regulation of blood pressure in healthy subjects is tightly controlled by the autonomic nervous system, and that any changes, such as increased blood flow or venous pooling will be mitigated by neurohormonal pathways.

Dynamic FES Modality

Our study found that combing FES with passive mobilization significantly increases blood flow when compared to isometric FES or passive mobilization separately. This is important, since many studies in SCI rehabilitation have focused on the use of isometric FES for improving blood flow, but none have assessed the effects of the combination of FES with passive movement therapy during head-up tilt. One study does note that higher blood flow is possible during dynamic exercise, as locomotive movements will cause muscle fiber length changes and thereby produce enhanced skeletal muscle pump activity. (19) Our finding is further strengthened by two more studies that assessed the differences in skeletal muscle blood flow during isometric and dynamic exercise. In the first study, (36) dynamic exercise was found to improve blood flow in the quadriceps femoris by 61% when compared to isometric exercise. In the second study, (37) hemodynamics functions of healthy subjects was enhanced during isometric FES combined with voluntary tip-toe contractions as compared to each independent modality.

The muscle pump should be most efficient under dynamic FES conditions for two reasons. First, we understand that blood flows freely during the period of muscle relaxation and is obstructed during the period of muscle contraction. Thus, optimal flow should occur during normal gait, where 60% of the stride pattern is spent in the stance phase and 40% during the swing phase. (38) Additionally, muscle contractions during isometric FES will involve simultaneous contraction of all the muscle fibers being stimulated, whereas, during dynamic movement, the muscle fibers are activated on unique time frames during the contracting and relaxing phase of the stride pattern. This enhances blood flow as the individual fibers are contracting on a physiologically relevant time scale. Compared to isometric FES and passive mobilization, dynamic FES is the best model to represent this motion as it combines both movement and muscle fiber activation.

Determinants of Blood Flow

The major determinants of muscle blood flow during exercise are workload and muscle metabolic rate. It is known that skeletal muscle blood flow during exercise is closely related to power output, regardless of subject's exercise capacity or training status. (39) Thus, by simply increasing the workload during exercise, one can increase muscle blood flow. In this study, we were unable to measure power output. However, it should be clear that dynamic FES provides a higher workload than passive mobilization or isometric FES.

Additionally, sustained exercise, will release metabolites that will cause local vasodilatation and capillary recruitment, leading to an increase in muscle blood flow. (40) Consequently the greatest increase in tissue metabolism, which occurs during dynamic FES, will correlate with the highest increase in blood flow.

Imaging Venous Return using Doppler Ultrasound

The present study also demonstrates the possibility of measuring venous flow in the assessment of OH by using Doppler ultrasound. Ultrasound imaging of the inferior vena cava diameter has been established for the evaluation of venous return under orthostatic stress. (26-29) In our study we chose to image the inferior vena cava cross-sectional area for enhanced resolution. A limitation of the ultrasound imaging method is the possibility of motion artifacts in ultrasound data due to lower limb movement during dynamic exercise. To overcome this, steps were taken to secure subjects to the tilt table and fix the ultrasound probe (described in protocol). Another limitation is occlusion of the femoral and brachial vessels by the tilt table harness, which we attempted to avoid using padded harness straps. Although several subjects commented about feeling occluded, IVC_{CSA} imaging did not show venous flow reduction or obstruction. In future studies, it would be important to develop a harness system which does not occlude lower limb blood flow during HUT maneuvers. Nevertheless, because, the same imaging technique and tilt duration were used for all subjects, changes in intra-subject blood flow were consistent.

LIMITATION OF THIS STUDY

Two experiments were conducted per day (1600h – 1900h and 1900h – 2200h) in quick succession over the course of two weeks. There were time constraints resulting from accessing the ultrasound equipment and running the experiment during non-clinical hours. As a result, the study used a small sample size of 10 subjects, which may have hindered statistical analysis. The automated wrist monitor (Omron HEM-637) was found to have an accuracy of ±5 mm Hg for blood pressure and ±3 beats per minute for heart rate. (6) Additionally, automated blood pressure monitors are known to be susceptible to artifacts caused by limb movement and muscle tensing. Although every effort was made to prevent arm movement, movements sometimes were observed when subjects adjusted or flexed the arm or hand to prevent blood pooling. For future studies, a better protocol is required to immobilize the monitored limb to prevent muscle activity and muscle tension. In addition, future experiments should use a clinically certified BP and HR monitor, such as the Finopres (FMS, Amsterdam), which can perform real time beat to beat measurements.

In this study, gastrocnemius and quadriceps muscles were stimulated since doppler analysis of femoral flow found the activation of these three muscles caused the greatest increase in flow (Appendix A). A definitive analysis of each muscle's contribution to hemodynamic by means of a femoral doppler and tilt table study would be valuable as this would determine the muscles required for the proper activation of the skeletal muscle pump. To date, no study exists which characterizes this. Additionally, the level of contractile force was not controlled during electrical stimulation. Rather stimulation intensity was adjusted to each subject's pain threshold. This may cause variability in muscle pump activity leading to more effective muscle pumping in certain subjects while less effective pumping in others. This should be investigated for clinical significance.

CONCLUSION

There has been considerable interest in the use of isometric FES for the regulation of orthostatic hypotension. A recent report observed that isometric FES accompanied tilt in SCI patients can regulate haemodynamics and prevent OH supports this notion. (4) This present investigated the effect of isometric FES, passive mobilization and dynamic FES on the regulation of haemodynamic stability during orthostatic stress experienced.

The ability of the skeletal muscle pump in attenuating the response to orthostatic stress was investigated. This study demonstrates the potential use of dynamic FES over isometric FES and passive mobilization therapy in improving orthostatic toleranc in healthy subjects. This method could potentially be used in clinical practice as a means of improving orthostatic tolerance during the acute phase of SCI. Future studies are needed to evaluate the benefit of dynamic FES in individuals with SCI.

FUTURE WORK

This study found that dynamic FES was more effective than isometric FES for maintaining haemodynamic state during orthostatic stress. This is an important conclusion and can have profound importance in the field of SCI rehabilitation, since no research has focused on the use of dynamic FES in the maintenance of haemodynamic state in individuals with SCI.

As a next step it will be important to validate these findings in the SCI population. This will involve performing a power calculation to calculate the effective sample size for satisfying the statistical analysis. This will be important to prevent Type I error in the data analysis and in determining the number of subjects necessary. Determining recruitment numbers will be critical for planning and scheduling in the next phase, as the study will need to assure that an adequate number of candidates who satisfy the inclusion criteria exist to perform the experiment.

The experimental setup should be designed to prevent haemodynamic occlusion for long periods of head up tilt. In the feedback from the present study, several subjects complained of feeling occluded when tilted using the harness system. In the analysis of the inferior vena cava blood volume by ultrasound we could not see any major reduction in blood volume that signifies occlusion. Nevertheless, it would be interesting to determine if circulatory haemodynamics can be further improved by a reduction in the harness restrictions.

ACKNOWLEDGEMENTS

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APPENDIX A: FEMORAL VEIN FLOW RATE STUDY

Previous experiments investigating involuntary leg muscle activity have focused on the quadriceps, hamstring, tibias anterior and gastrocnemius muscles. These muscles were targeted since they are believed to be involved in activating the muscle pump. However a literature search could not find any information on the effect of each muscle in producing the skeletal muscle pump action. Furthermore, no studies justified the rational behind their muscle selection. Therefore, to properly analyze the effectiveness of FES for the current study, the question of muscle selection needed to be addressed a priori.

An experiment to measure femoral venous flow due to maximal involuntary contractions of the quadriceps, hamstring, tibias anterior and gastrocnemius muscles was conducted. The study quantified the maximal flow rates of various FES stimulation routines measured at the femoral vein by ultrasound doppler method. Due to the sensitive location of the femoral vein, measurements were only available from one health individual. The subject was seated, with both legs elevated. During the experiment, the legs remained relaxed and motionless. A recovery period of one minute was allowed between successive measurements. The identical FES stimulation protocol was used (biphasic waveform with a 30 Hz frequency, 300 us pulse width, a duty cycle of 2 seconds on, 2 seconds off).

The flow rate experiment (Figure A-1) revealed that a maximal flow rate of 49 cm/s were obtained when the quadriceps and gastrocnemius experienced contractions out of sync. This caused a muscle pumping action where gastrocnemius contraction occurred during quadriceps relaxation and vice versa. This muscle combination is believed to be similar to normal gait and therefore physiologically relevant. For future studies, additional subjects are needed to verify this observation.

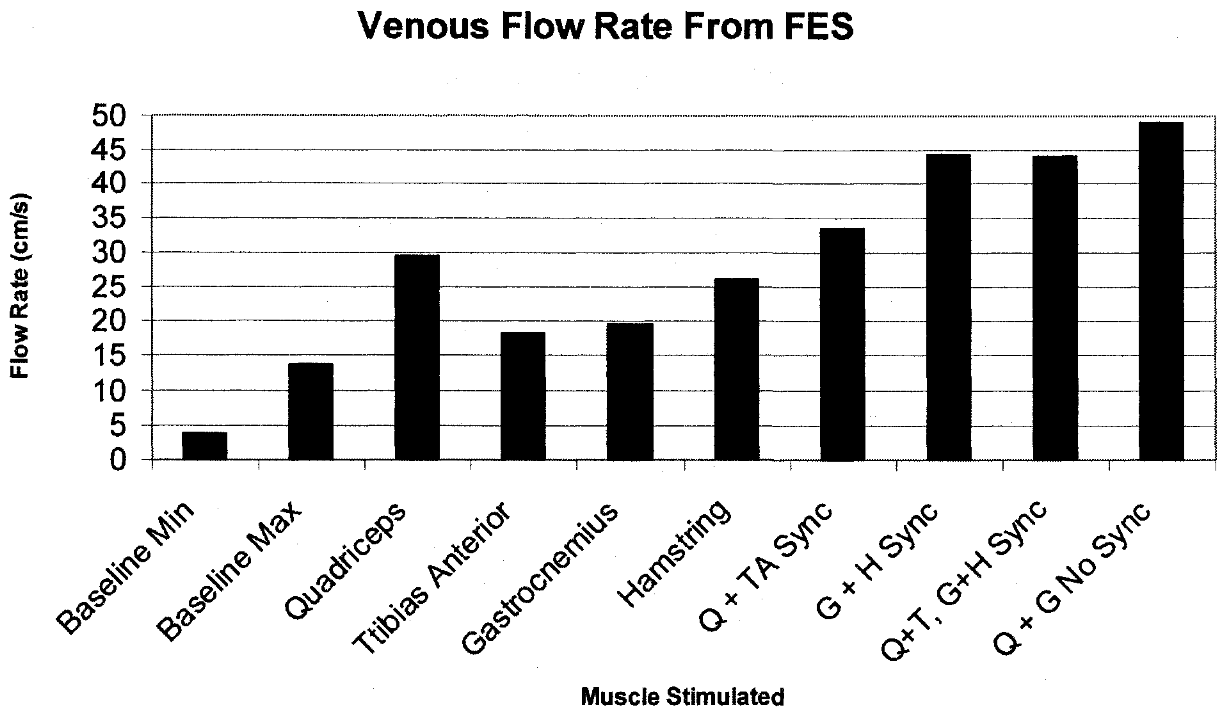

Figure A-1: Venous flow rate characteristics resulting from involuntary stimulation of specific leg muscles. N=1.

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ETHICS PROTOCOL SUBMISSION

Effects of Functional Electrical Stimulation on Venous Return during Orthostatic Stress in Man

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January 25, 2006

1. Background, Purpose and Objectives

1.1 Background & Physiology

The venous system serves as a major reservoir of blood, containing 64 percent of the systemic circulation. When intra-vascular volume increases, it is predominantly distributed into the venous system, which is more distensible and has greater compliance. When venous distensibility is reduced, blood volume is redistributed to the arterial system where it results in an increase in blood pressure.

In an upright posture, gravity will exert positive pressure on the arterial and venous circulation below the level of the heart, known as central venous pressure (CVP). Since pressure increases by 1 mmHg for every 1.36 cm, the arterial pressure at the level of the foot (120 cm below the heart) can approach +90 mmHg. Venous pressure at the level of the foot is normally 25 mmHg in a walking adult. This reduction in pressure between the venous and arterial system results from one way valves arranged so that the direction of venous blood flow is always towards the heart. In walking, muscle contracture of the legs help propel blood towards the heart. This pumping mechanism is known as the venous pump. When standing still, the venous pump is inactivated, and after 30 seconds, the venous pressure at the level of the foot can approach 90 mmHg above CVP. After 15 minutes of standing, 10 - 20 percent of the blood volume can be lost from the circulatory system as increased capillary pressure causes fluid to leak into the tissue space.

Orthostatic hypotension (OH) is defined as a sudden fall in blood pressure occurring when a person assumes an upright posture. OH can result from a low volume of circulatory blood, known as hypovolemia. The condition of OH is especially prevalent in spinal cord injured patients who, due to their injury, may suffer from hypovolemia or circulatory problems. These patients do not have function below the site of injury and therefore can no employ venous pumping. The condition of OH can be simulated in able bodied subjects if they experience head up tilt while lower limb movement is constrained.

1.2 Purpose

Previous studies investigating the effects of orthostatic loading conditions in ABS and spinal cord subjects (SCI) found that lower limb muscle contraction was an important factor in regulating OH conditions. (Thrasher et al., 2005b, Faghri & Yount, 2002) Faghri & Yount (2002) discovered dynamic standing, as characterized by voluntary tiptoe contractions, lead to a 2% increase in cardiac output for ABS after 5 and 30 minutes of standing. The authors concluded that FES may be beneficial for increasing tolerance to orthostatic stress.

The purpose of this study is to characterize the venous return (VR) in able bodied subjects (ABS) who experience orthostatic loading (head up tilt) under two conditions: a) FES stimulation of the gastrocnemius and quadriceps or b) no FES stimulation. From this study we can quantify the importance of FES on reducing OH conditions.

1.3 Objective

This study will provide a baseline measurement of venous return in ABS to be used as a baseline for follow-up investigations in patients with various autonomic neurological lesions. The establishment of a normal range of response in venous return in healthy subjects is important as previous studies indicating FES is beneficial for the regulation of orthostatic stress in SCI did not have adequate ABS controls or lacked ABS controls completely. (Raymond J et al., 1999; Chao & Cheing, 2005; Faghri & Yount, 2002)

2. Research Methodology

2.1 Experimental Protocol

This will be a pilot study, where subjects act as their own controls. Each subject will participate in two testing conditions: head-up tilt with electrical stimulation and head-up tilt without stimulation. The order of the test will be decided by coin flip. The subject will refrain from consuming food, caffeine, nicotine and alcohol for 8 hours before the study.

Each subject will start in the supine position on the tilt-table. An assessment of VR while in the supine position will be recorded and used as the baseline measurement. The subject will either receive FES or no stimulation (NS). The subject will experience head-up tilt of 70 degrees for 12 minutes, while continuously receiving FES or NS. VR data will be collected at 3 intervals; initial head-up tilt and after 5 and 10 minutes. Stimulation will end (if applied) and the subject will be brought to the supine position. After the subject achieves baseline VR values, the experiment will be repeated with the other condition.

2.1.1 Venous Return Measurement

Venous return (VR) is the blood flowing back to the heart. Under normal conditions VR is the either the limiting factor for cardiac output (CO), or drives CO such that CO is equal to VR. Cardiac output will be measured non-invasively using an automated non-invasive CO2-based Fick method developed by Dr. Joseph Fisher and colleagues at the University Health Network. The method is similar to that available commercially from Respironics in the NICO2 system. The NICO2 is designed for intubated, paralyzed and ventilated subjects. Dr. Fisher's device has been designed to carry out the same method in spontaneously breathing subjects. The method requires the subject to breathe via modified commercial sequential gas delivery breathing circuit (Hi-Ox80, Viasys Healthcare, Yorba Linda CA). The circuit is modified to provide fresh gas (air or oxygen) at a fixed rate and previously exhaled gas if the subject increased his/her ventilations above the provided gas flow. During steady state, the subject is provided sufficient fresh gas for his respiratory requirement. The test consists of a transient reduction in the fresh gas for about 5 breaths (or 20-30 s) resulting in partial rebreathing of previously exhaled gas. The effect of the change in fresh gas flow is undetectable by most subjects. The physiologic effect is equivalent to holding the breath for 10-15 s. After the reduction in fresh gas flow the patient is provided with a brief period of excess fresh gas flow to make up any deficits in gas exchange. A new steady state is then re-established and the cycle can be repeated indefinitely. The brief period of reduction in fresh gas flow is sufficient to calculate the CO and hence VR. The test has been performed in many healthy subjects over the last 3 years and recently in 135 fully monitored subjects immediately post open heart surgery. There were no long term or short term effects of this testing on any of the subject. (Preiss, 2005)

2.1.2 Functional Electrical Stimulation Protocol

FES is used to artificially contract the musculature of the lower limbs and has been shown to improve VR. (Faghari & Yount, 2002, Man et al., 2003) This study will use the Compex FES stimulator (Compex SA, Zurich) which functions by transcutaneous electrical stimulation of targeted muscles by the use of surface electrodes. (Keller et al., 2002) Stimulation is well documented in previous studies, and there are no long term effects of testing. Short term effects include muscle fatigue and soreness. (Thrasher et al., 2005a; Popovic et al., 2005b)

The stimulator is programmed to produce a biphasic waveform with a 30 Hz frequency, 300 us pulse width, a duty cycle of 2 seconds on and 2 seconds off and a maximum amplitude of 125 mA. These values are in accordance with previous studies. (Thrasher et al., 2005b; Popovic et al., 2005a; Popovic et al., 2005b) The gastrocnemius and quadriceps will be stimulated out of phase, so that gastrocnemius contraction leads to quadriceps relaxation and vice versa. This stimulation protocol has been shown to result in a 340 percent increase in venous blood flow when compared to baseline measurements. (Figure B-1)

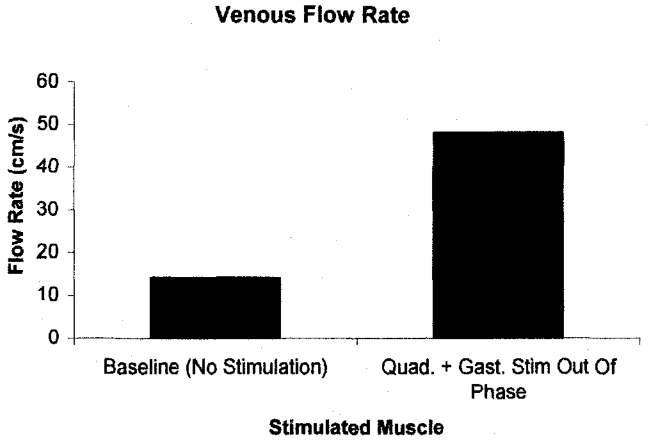

Figure B-1. Venous flow rates. A flow rate of 14 cm/s was observed during no stimulation. A flow rate of 48 cm/s was observed when quadriceps and gastrocnemius were stimulated out of phase with the protocol in § 2.1.2 (*Unpublished Data*)

3. Participants

3.1 Selection of Subjects

An advertisement will be posted for able bodied subjects to participate in this study.

3.2 Inclusion criteria:

- Male
- Pre-menopausal female
- subjects from 19 to 50 years of age
- taking no medication
- no history of vascular, respiratory, renal, liver, endocrine or neuron-muscular disease
- non smokers.

3.3 Exclusion criteria:

- Subjects who do not sign the letter of consent
- Subjects with reservations or who experience discomfort from involuntary contractions caused by electrical stimulation
- Subjects who have a poor understanding of the research goals
- Subjects who have skin rash, allergy or wounds at the locations where stimulation electrodes will be placed
- Not within 10% of ideal body weight

4. Recruitment

Subjects will be recruited by a posted advertisement. A research team member will inform the subject about the research purpose, the identity of the researcher, the expected duration and nature of participation, the research procedures and foreseeable risks and benefits associated with participation in the study. Once all the subject's questions pertaining to the study have been answered, the subject will be given a written consent form to read and sign.

5. Risks and Benefits

5.1 Risks

Rapid head up tilt may lead to dizziness and light headedness. It is very unlikely that a healthy, active subject would lose consciousness. Should the subject feel unwell, the tilt table will be reclined.

The electrical stimulation results in a slight tingling sensation which some subjects may find objectionable. The stimulated, involuntary muscle contractions may also be unpleasant to some subjects. The electrical stimulation can be decreased to provide more comfort. Failing that, subjects may withdraw from the study.

5.2 Benefits

There are no benefits for the subject.

6. Privacy and Confidentiality

"Guidelines for Data and Privacy Protection at the Rehabilitation Engineering Laboratory" are attached to this document in Appendix A. These guidelines will be followed in the study.

7. Compensation

None

8. Conflicts of Interest

The method of measuring cardiac output has been developed by Dr. Joseph Fisher and his group. Applications for patents on the method and apparatus have been applied for under the guidelines of UHN intellectual property guidelines. The owners of the patents is a corporate group established in cooperation with the UHN Research Business Development office under Mr. Bob McArthur and includes Dr. Fisher. Should the cardiac output measurement device become a commercially successful device, Dr. Fisher, and the UHN may benefit financially.

9. Informed Consent Process

"Informed Consent Document" that consists of information letter and consent form is attached to this document in Appendix B.

10. Additional Ethics Reviews

This research project is submitted to the Toronto Rehab Ethics Review Committee, the University of Toronto Ethics Committee, and the University Health Network Ethics Review Committee.

11. Contracts

Not applicable.

12. Clinical Trials

Not applicable.

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Feb 10/06

Informed Consent Form

Study: Effects of Functional Electrical Stimulation on Venous Return during Orthostatic Stress in Man

Researchers: Dr. Adam Thrasher[1], Lorne Chi[1], Alexandra Mardimae[2], Cathie Kessler[2], Dr. Milos Popovic[1], Dr. Joseph Fisher[2]

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Toronto General Research Institute

Summary of Study:

This study will characterized the effect of functional electrical stimulation (FES) on the venous blood flow in able bodied subjects who experience head up tilt. The study is a pilot study where each subjects acts as own controls. Each subject will participate in two testing conditions while experiencing 70 degrees head up tilt: a) FES stimulation of the gastrocnemius and quadriceps or b) no stimulation. The duration of each study will be 12 minutes. Venous return, heart rate and blood pressure will be recorded at 0, 5 and 10 minutes into the study by using a non-invasive respiratory device.

Duration of Study:

The study will last a maximum of 1.5 hour.

Please arrive 5 minutes before your scheduled session.

Participant Requirements:

Participants must refrain from consuming food, caffeine, alcohol or nicotine for 8 hours before the study.

Inclusion criteria:

- Male
- Pre-menopausal female
- subjects from 19 to 50 years of age
- taking no medication
- no history of vascular, respiratory, renal, liver, endocrine or neuron-muscular disease
- non smokers.

Exclusion criteria:

- Subjects who do not sign the letter of consent
- Subjects with reservations or who experience discomfort from involuntary contractions caused by electrical stimulation
- Subjects who have a poor understanding of the research goals
- Subjects who have skin rash, allergy or wounds at the locations where stimulation electrodes will be placed
- Not within 10% of ideal body weight

Frequently Asked Questions:

What is FES?

Functional electrical stimulation (FES) is a method of causing involuntary contractions of muscles by stimulating motor neurons. FES is used by neurological patients to improve function and by elite athletes to enhance performance. This study will use transcutaneous electrical stimulation, in other words, electrical stimulation by means of electrodes attached to the skin.

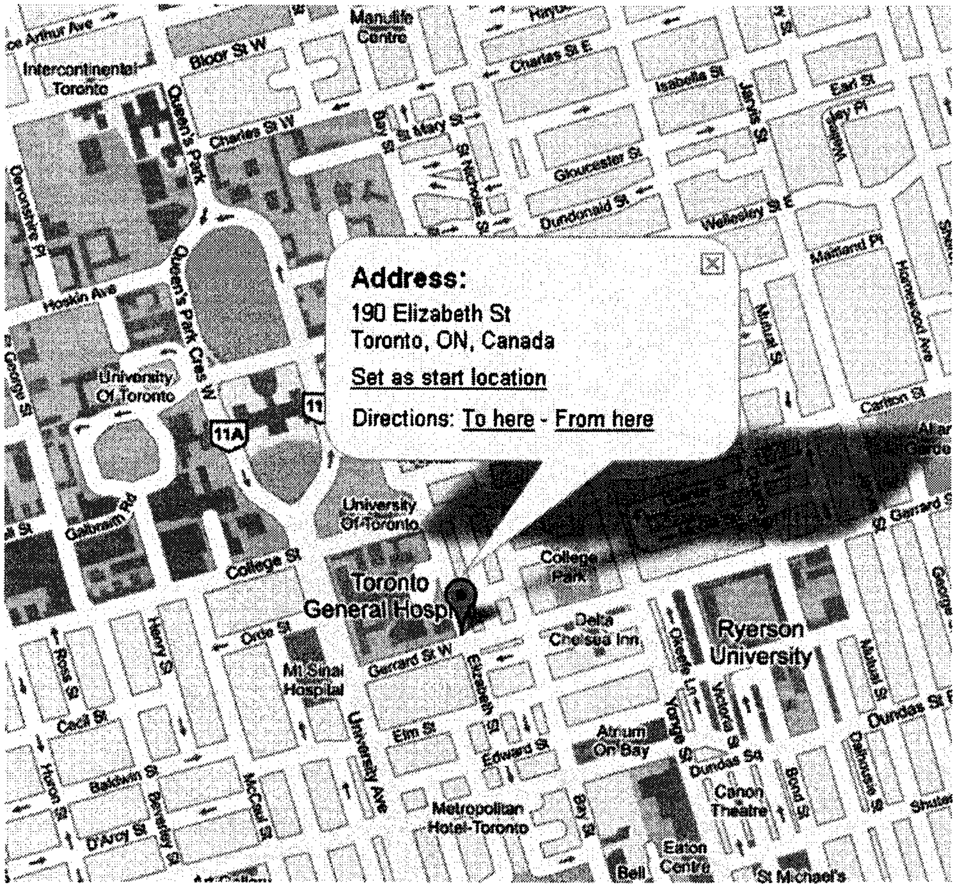
Will FES shock me?

FES will **not** “shock” you. FES therapy uses large electrodes which distribute the current density over a large surface. This way you can not be “shocked”.

What is the goal of this study?

The study aims to characterize the venous flow rate of able bodied subjects which will provide a baseline measurement for future studies on neurological patients.

Study Location:



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Email:	Lorne.Chi@utoronto.ca

Informed Consent Form:

I ________________________________ understand and consent to the study conducted by Thrasher et al. I meet all the inclusion requirements for this study and am willing to participate. I understand that the study requires me to refrain from consuming food, alcohol, caffeine and nicotine for 8 hours prior to my participation to produce meaningful results and will do so on the day of the study.

Signature	Witness
______________________________	___________________________________
Date: _________________________	Date:________________________________

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Guidelines for Data and Privacy Protection at the Rehabilitation Engineering Laboratory

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This document outlines the policies and procedures at the Rehabilitation Engineering Laboratory (REL) pertaining to patients and subjects' (further in the text subjects) data and privacy protection.

Guidelines:

1. Subject's name, date of birth, and patient number, if available (in the case of able-bodied subjects the patient number is not applicable), have to be stored separately from the remaining subject's data, such as digital and hard copy versions of measurement data, X-ray pictures, diagnosis, etc. To ensure this an excel file, called ***key file***, that contains subject's name, date of birth, patient number, and REL code (associated with the subject) has to be created. The key file has to look as follows:

No.	Subject's Name	Date of Birth	Patient Number	REL Code
1	Jake Snake	September 6, 1998	774344	AAAA
2	Mike vanDyke	June 2, 1966	Not Available	AAAB
3	Silvija Boreli	January 13, 1972	452212	PKLD

All research members at REL will use only REL code to store data pertaining to the subject. **Subject's name, image, date of birth and patient number must not appear in the files stored under the REL code. The REL code and the name of the patient to whom this code is assigned to must not be related, i.e. one should not be able to**

correlate the REL code with the subject's name, date of birth or patient number. Both hard copies and digital data will be stored under the REL code name. For example, all measurement data, spread sheet files, word files, etc. for subject Mike vanDyke, who has REL code AAAB, should be stored in the folder AAAB as files which names would always start with the following four letters aaab. It is left to the user to fill the reminder of the file name, as he/she desires. Examples: aaab_exp001.dat, aaab_diagnosis.doc, aaabblabla.txt, etc. **Hard copy documents pertaining to the subject should be all stored in folders (physical folders) which will be labeled with the REL code.** For example, all hard copy data pertaining to subject Mike vanDyke will be stored in the folder which name is AAAB. **These folders should not contain the subject's name, image, birth date and patient number, and can be stored in regular cabinets that are accessible to all REL members.**

2. **The above mentioned key file will be stored on the different media from the subjects' data, and will be accessible only to the designated person at REL.** For example, the key file can be stored as an electronic file on a zip drive or as a hand written spread sheet. The key file will be locked in a filing cabinet belonging to the designate person. The key file, regardless of the media that is used to record it, has to be securely stored away from the remaining subjects' data. **Only the designated person will be allowed to handle the key file and to assign REL codes to subjects.**

3. **Files or folders starting with the REL code name shall not contain subject's name, image, birth date and patient number.** Such files or folder can only contain the birth year and the subject's sex, but not the complete date of birth.

4. **Folders that contain names, birth date, image and patient number will be kept in the cabinet that will be under supervision of the person in charge of data protection. The cabinet has to have a lock and has to be locked every evening. Only the authorized personnel can retrieve the folders with the hard copy data from this cabinet after signing up. In the event a folder or a document from the folder is missing, the person who has signed it out last will be considered responsible and accounted for the missing folder or document.**

5. **Video tapes containing subject's image and subject's photographs will be stored and protected in the same way as items discussed in 4.**

6. Software folders with REL codes (for example AAAB) will be stored at designated hard drives. These hard drives will be backed up on regular basis and will be protected using a firewall. In the event the firewall is not functioning, the hard drives with the subjects' data have to be disconnected from Local Area Network (LAN) or Wide Area Network (WAN).

7. **In the case subject's data has to be published one has to ensure that the subject's name, face, complete date of birth and patient number do not appear in the document. The year of birth and subjects sex can be disclosed.**

8. **After the study is completed and the results of the study are published, the subjects' data will be stored at REL premises for at least five years.** After five years of the study's completion the REL reserves rights to purge the data.