Cardiovascular Response to Dynamic Functional Electrical Stimulation During Head-up Tilt

by

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Abstract

Orthostatic hypotension (OH) is a prevalent condition among individuals with spinal cord injury (SCI). After an injury, OH often reduces the benefit of neurorehabilitation and also prolongs periods of inactivity that lead to secondary complications. This study investigated whether the cardiovascular response to head-up tilting can be improved using functional electrical stimulation (FES) and rhythmic passive movements of the lower extremities. Participants with high thoracic and cervical SCI were recruited. While the participants were tilted head-up to 70 degrees, four conditions were applied in a random sequence: 1) no intervention, 2) rhythmic passive leg movements, 3) isometric FES, and 4) a combination of FES and passive leg movements. The measured cardiovascular parameters indicated that a combination of FES and passive leg movements induced the most desirable response to head-up tilting. The proposed intervention will enable more individuals with SCI to participate in beneficial neurorehabilitation that uses a novel tilt table.

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List of Abbreviations

AD – Autonomic dysreflexia

CSA_{IVC} – Cross-section area of the inferior vena cava in the transverse plane

DBP – Diastolic blood pressure

DFES – Dynamic FES (combination of STEP and FES of the lower extremities)

EMG – Electromyography

FES – Functional electrical stimulation

HR – Heart rate

HUT – Head-up tilting without intervention

IFES – Isometric FES of the lower extremities

IVC – Inferior vena cava

OH – Orthostatic hypotension

SBP – Systolic blood pressure

SCI – Spinal cord injury

STEP – Passive stepping (imposed rhythmic passive movements of the lower extremities)

SV – Stroke volume

SVR – Systemic vascular resistance

Chapter 1: Introduction

1.1 Motivation

Orthostatic hypotension (OH) is a problematic condition for individuals with spinal cord injury (SCI). Individuals with SCI, especially in the acute or sub-acute phase, are more susceptible to OH if their injury is in the upper thoracic or cervical region of the spine. Because cervical injuries account for the majority of SCI cases in North America, many individuals with SCI can benefit from effective prevention of OH.

Available methods for managing OH are often inadequate, especially if any method is used in isolation (i.e., not in combination with other methods). Without effective management of OH, individuals with SCI will experience greater challenges in performing tasks that involve orthostatic stress. For example, OH can hinder the progress of rehabilitation because many of the physiotherapy and occupational treatments involve orthostatic stress. Without adequate tolerance for orthostatic stress, the range of administrable therapies becomes limited, reducing the overall benefits of rehabilitation. Furthermore, in acute and sub-acute phases of SCI, orthostatic intolerance can prolong periods of bed rest or inactivity, which lead to secondary complications such as bone loss, muscle atrophy, and deep vein thrombosis. Thus, improving orthostatic tolerance is an important objective of early SCI therapy.

A novel tilt table (Erigo®, Hocoma AG, Switzerland) has been designed to assist in gait rehabilitation and to help improve the orthostatic tolerance of individuals with SCI. This study proposes the use of functional electrical stimulation, in combination with the novel tilt table, to improve the cardiovascular response of individuals with SCI to head-up tilting. If the proposed intervention is effective, more individuals with SCI will be able to incorporate head-up tilting in their therapy and improve the quality of rehabilitation.

1.2 Research Method in Brief

This study investigated the individual with combined effects of functional electrical stimulation (FES) and passive movements of the lower extremities for preventing SCI-related orthostatic hypotension. Four conditions were applied to individuals with SCI during a 70-degree head-up tilt: 1) no intervention, 2) imposed passive movements of the lower extremities, 3) isometric FES of the lower extremity muscles, and 4) combination of imposed passive movements and FES. The conditions were applied in a random sequence, and each condition was preceded and followed by a ten-minute supine rest. Throughout all test conditions and supine rests, the beat-to-beat blood pressure, heart rate, stroke volume, and systemic vascular resistance were non-invasively measured. The transverse images of the inferior vena cava were also recorded to indirectly assess the changes in venous return. When the applied test condition did not involve FES, the electromyograms of the leg muscles were recorded.

1.3 Hypothesis

This study's experimental protocol was validated by a previous study [3], which suggested that a combination of FES and passive leg movements (as opposed to FES or passive leg movements alone) induced the greatest venous return in able-bodied participants during a head-up tilt. Another study [4] has also indicated that a combination of FES and passive leg movements induced better cardiovascular responses to orthostatic stress in an upright standing posture, compared to FES without movements. This study's hypothesis was that the combination of FES and passive leg movements, tested by previous studies [3,4], would improve the cardiovascular response of individuals with SCI to a 70-degree head-up tilt. Specifically, we hypothesized that the proposed intervention would maintain a normal blood pressure during head-up tilting, and ultimately prevent the symptoms of orthostatic hypotension by maintaining cerebral perfusion.

1.4 Roadmap of the Thesis

This document consists of six chapters. Chapter 1 introduces the study by describing its motivation and hypothesis. This chapter also briefly describes the study’s methodology. Chapter 2 contains relevant background knowledge for the study: normal and pathological (post SCI) mechanisms of autonomic cardiovascular control, orthostatic hypotension, and technologies used in the study. Chapter 3 describes the study’s methodology in detail. This chapter describes participants, experimental protocol, apparatus, and post processing of the obtained data. Chapter 4 summarizes the experimental results, and Chapter 5 discusses the results. Chapter 6 concludes the study with a suggested future direction for this study. The complete bibliography is provided at the end of this document.

Chapter 2: Background

2.1 Normal and Pathological Cardiovascular Control

2.1.1 Normal Autonomic Cardiovascular Control

The arterial blood pressure is determined by cardiac output and peripheral vascular resistance, which are controlled by the sympathetic and parasympathetic nervous systems.

The sympathetic nervous system affects both cardiac output and peripheral vascular resistance. Sympathetic stimulation increases cardiac output by increasing the rate and force of myocardial contractions, which can be doubled under strong stimulation [5]. Vascular resistance is regulated by the continuous partial constriction of arteries and arterioles [5]. The constriction is induced by continuous sympathetic stimulation, known as sympathetic vasoconstrictor tone [5]. The sympathetic nerves also innervate the veins, whose volumes decrease upon stimulation [5]. Decreasing the venous volume will facilitate venous return, which helps to maintain the blood pressure.

Unlike the sympathetic nervous system, the parasympathetic nervous system mainly innervates the atria of the heart. Due to this anatomy, parasympathetic stimulation can significantly decrease heart rate but only slightly decrease the contractile force of the myocardium [5,6]. Also, the parasympathetic nervous system has almost no effect on the systemic vasculature [5,6].

2.1.2 Impaired Autonomic Cardiovascular Control after SCI

An injury of the spinal cord impairs the sympathetic control of the cardiovascular system. The impairment can be explained by several mechanisms, including the loss of supraspinal regulation and depressed sympathetic tone below the injury level [6,7]. Inhibiting the sympathetic stimulation can decrease both the force and rate of myocardial contractions by as much as 30% below normal, and decreased cardiac output is compounded by the impaired sympathetic vasoconstrictor tone [5].

The sympathetic nerve fibers that innervate the heart exit the spinal cord between T1 and T5 levels, while the fibers innervating the peripheral vasculature exit between T1 and L2 [5,6]. This explains why individuals with higher levels of injury have more severely impaired sympathetic cardiovascular control.

A spinal cord injury (SCI) does not affect parasympathetic cardiovascular control because the parasympathetic nerves that innervate the heart (vagus nerves) originate in the brain stem and do not pass through the spinal cord [5,6]. Thus, SCI results in impaired sympathetic control and intact parasympathetic control of the cardiovascular system.

2.2 Normal and Pathological Cardiovascular Response to Orthostatic Stress

Upon postural change from the supine to the upright standing posture, 500 to 1000 ml of blood will gravitate towards the lower extremities within the first ten seconds [8]. Furthermore, the increased transmural pressure of the capillaries causes fluid in the blood to escape into tissue space, gradually decreasing the plasma volume [8]. This pooling of the blood and decrease in the plasma volume reduces venous return, leading to reduced stroke volume and, ultimately, decreased arterial pressure. Normally, the short-term compensatory mechanism to this gravity-induced orthostatic stress consists of vasoconstriction and an increase in heart rate. However, vasoconstriction is a more important compensatory mechanism, and increasing heart rate alone is insufficient to maintain arterial pressure [8]. In a healthy individual with a centrally mediated sympathetic nervous system, the baroreflex plays a major role in the short-term regulation of blood pressure. Normally, when blood pressure falls (e.g., due to standing), the baroreflex elicits sympathetic stimulation of the heart and peripheral vasculature within seconds [5,6].

If the upright posture is sustained, arterial pressure will be maintained by additional mechanisms of vasoconstriction, including the renin-angiotensin system and the release of vasopressin [8]. The renin-angiotensin system results in the release of angiotensin II, a powerful vasoconstrictor [5]. Angiotensin II also causes the kidneys to excrete less salt and water, and this will increase arterial pressure in the long-term [5]. Vasopressin is both an antidiuretic hormone and a vasoconstrictor (more powerful than angiotensin II) [5]. In addition to vasoconstriction, voluntary muscle contractions in the lower limbs can induce venous return to maintain cardiac output.

In individuals with SCI, postural vasoconstriction occurs via local mechanisms that do not require supraspinal regulation: venoarterial reflex, which is triggered by an increase in the transmural pressure of small veins; and arteriolar myogenic reflex, which is triggered by an increase in the arteriolar transmural pressure [9-11]. The latter is possibly the more important mechanism in individuals with SCI [10]. However, these local mechanisms may be insufficient to prevent orthostatic hypotension. Also, the paralysis of lower limbs muscles will have a significant impact during sustained upright standing or a head-up tilt. For individuals with cervical SCI, a common response during orthostasis involves a gradual decrease in blood pressure and a gradual increase in heart rate [6,12].

2.3 Orthostatic Hypotension

2.3.1 Definition of Orthostatic Hypotension

Orthostatic hypotension (OH) is a condition associated with symptoms of cerebral hypoperfusion such as dizziness, lightheadedness, and fainting [6,7,13-16]. Regardless of these symptoms, orthostatic hypotension can be defined by a rapid decrease in blood pressure: either a minimum decrease in the systolic blood pressure by 20 mmHg or a minimum decrease in the diastolic blood pressure by 10 mmHg [6,13]. A widely used definition of OH further specifies that these changes are observed within three minutes of assuming an upright standing posture from supine [6,13].

2.3.2 Prevalence of Orthostatic Hypotension after SCI

Regardless of the completeness of the injury or the duration of bed rest prior to mobilization, individuals with tetraplegia are more susceptible to OH [6,16]. In one study [17], 57.1% of participants with SCI experienced OH during a head-up tilt, and all but one that experienced OH had injuries above T5. This selective susceptibility can be explained by the greater impairment of the sympathetic cardiovascular control in individuals with higher levels of injury.

According to several epidemiological studies, cervical injuries account for 55 to 75% of the investigated cases of SCI in North America [18-20]. As OH occurs more frequently in individuals with cervical SCI, the prevalence of OH among individuals with SCI is clear. Indeed, one study [16] found that 73.6% of mobilization maneuvers during SCI rehabilitation resulted in OH. Furthermore, 58.9% of the maneuvers accompanied visible or self-reported symptoms of OH, and 33.3% of the maneuvers were perceived as being limited by OH.

2.3.3 Consequences of Prolonged Inactivity after SCI

OH can prolong periods of immobilization or limited activity. This leads to secondary complications such as bone loss, especially in the long bones of the lower extremities [21-23]; cardiovascular deconditioning [6,7,14,15], which involves decreased cardiac work capacity, hypovolemia, and impaired baroreflexes [5]; and atrophies and decreased fatigue resistance of paralyzed muscles, especially in muscles that normally bear body weight [24,25].

Atrophies of paralyzed muscles are largely due to disuse [24-26]. In addition to decreased mass, paralyzed muscles also change their composition: slow-twitch and fatigue-resistant (type I) fibers diminish, and fast-twitch and easily fatigued (type II) fibers become dominant [26,27]. The result is drastically reduced endurance of the paralyzed muscles [24].

2.3.4 Management of Orthostatic Hypotension without FES

Passive standing is a beneficial therapy that subjects individuals with SCI to orthostatic stress. Prolonged and frequent standing can improve cardiovascular responses to orthostatic stress [23] as well the perception of well-being [28]. In addition, the weight bearing from passive standing can reduce bone loss [22], hypercalciuria [29], incidences of urinary tract infections [23,30], spasticity [23], and chance of developing pressure ulcers. Similarly to passive standing, head-up tilting subjects individuals with SCI to orthostatic stress, and repeated exposure to tilting can improve orthostatic tolerance. Also, by adding sufficient weight bearing and rhythmic passive movements of the lower extremities, head-up tilting becomes an enhanced therapy for neurorehabilitation [31,32]. This idea for neurorehabilitation has inspired the design of the novel tilt table used in this study. The design of the novel tilt table is further discussed in Tilt Table under Apparatus.

In addition to treatments that improve the tolerance from repeated exposure to orthostatic stress, there are other methods of managing OH. Known methods include pharmacological intervention, increasing the extracellular fluid volume from increased intake of fluid and salt, preventing blood pooling by using abdominal binders or pressure stockings that apply abdominal or lower body positive pressure, and exercising under orthostatic stress [33,34].

Pharmacological intervention can have side effects and should be used strategically, in combination with non-pharmacological interventions [34,35]. Intake of fluid and salt alone is often inadequate, and so is applying positive pressure [34]. Upper body exercises are also ineffective in preventing orthostatic hypotension [33,34]. There is some evidence that passive leg movements may improve the cardiovascular response of individuals with SCI to orthostatic stress. However, a further investigation with well-controlled trials is needed.

2.3.5 Management of Orthostatic Hypotension with FES

Functional electrical stimulation (FES) has diverse applications in the fields of neuroprosthetics and rehabilitation [36-39]. By assisting or replacing voluntary muscle contraction, FES can generate functional movements that are otherwise impossible for individuals with SCI. As an intervention for OH, FES is used to maintain the arterial pressure by causing contractions of the leg muscles, which induces venous return under increased orthostatic stress.

The strength of FES is determined by three variables: pulse duration, frequency, and amplitude. Increasing any of these variables will increase the force of contraction, by either spatial (for pulse duration and amplitude) or temporal (for frequency) summation [38,39]. For transcutaneous FES, pulse duration should be between 100 and 700 μs, and frequency should be between 20 and 80 Hz. If the frequency is too low, stimulation only generates muscle twitches. The amplitude of stimulation depends on the application, but the normal range is between 10 and 100 mA.

Several studies have investigated the effectiveness of isometric FES on SCI-related OH [40-43]. All of these studies used isometric FES during passive standing or graded head-up tilting. In all studies, the electrical stimulation alternated between muscles to create a squeezing effect, which was designed to induce venous return. However, none of these studies monitored venous return as an outcome.

Some of the reviewed studies included participants with SCI below T6 level. This inclusion criterion would suggest that some participants had fully preserved sympathetic control of the heart. Also, these participants would have better sympathetic control of the systemic vasculature than participants with higher levels of injury. The more intact sympathetic cardiovascular control was, the less pronounced the contribution of FES-induced venous return would be.

In the reviewed studies, the applied isometric FES would be considered effective if the arterial blood pressure was well maintained under increased orthostatic stress. On the other hand, reduced stroke volume or increased heart rate would indicate that the FES intervention was ineffective. Normally, increased orthostatic stress would cause the blood to pool in the lower limbs, thus decreasing venous return. Consequently, stroke volume would decrease and the arterial blood pressure would fall. Without adequate compensatory mechanisms, such as voluntary contractions of the leg muscles, increasing the heart rate is the only remaining sympathetic compensation for the decreased blood pressure.

Table 1 summarizes the reviewed studies on various FES interventions for OH. Please note that studies on FES-assisted cycle ergometry have been excluded from the review, as cycle ergometry is used in a seated posture, which exerts considerably less orthostatic stress and weight bearing on the soles than a typical head-up tilt or passive standing. Also, the kinematics of cycle ergometry differs significantly from the kinematics of passive leg movements used in this study.

Table 1: Summary of studies on the effect of isometric FES to prevent orthostatic hypotension in individuals with SCI.

Reference number for study	Method of applying orthostatic stress	Stimulated muscles	Stimulation pattern	Number of participants with SCI below T6
[40]	Passive standing	Anterior and posterior muscles of shank and thigh	Alternating between shank and thigh muscles	3 of 13
[41]	Graded tilt up to 60°	Quadriceps and calf muscles	Alternating between quadriceps and calf muscles	2 of 5
[42]	Graded tilt up to 90°	Quadriceps and pretibial muscles	Alternating between quadriceps and pretibial muscles	None
[43]	Graded tilt up to 90°	Anterior and posterior muscles of shank and thigh	Alternating between shank and thigh muscles	None

The following paragraphs describe the effect of isometric FES on participants with SCI in each of the above studies. In the study by Faghri and Yount [40], participants with SCI that received isometric FES experienced significant increase in heart rate and significant reduction of stroke volume during passive standing. Despite these changes, the mean arterial pressure decreased only slightly, and it was relatively well maintained, even after 30 minutes of orthostasis. However, participants with SCI that did not receive FES experienced a slight increased in the mean arterial pressure, lower increase in heart rate, and significant increase in total peripheral resistance after 30 minutes of orthostasis. These results did not prove that isometric FES could improve the cardiovascular response of individuals with SCI to passive standing.

In the study by Elokda et al. [41], a head-up tilt with isometric FES resulted in higher systolic and diastolic blood pressures than a tilt without stimulation. However, even with FES, systolic blood pressure was lower by approximately 20 mmHg at a 60-degree tilt, compared to supine. Also, at a 60-degree tilt with FES, heart rate was higher by approximately 46% compared to supine. Therefore, this study did not demonstrate the efficacy of isometric FES as a means to prevent OH in individuals with SCI.

In the study by Sampson et al. [42], systolic and diastolic blood pressures decreased by approximately 20 mmHg during a 70-degree tilt with isometric FES, compared to systolic and diastolic pressures in the supine position with FES. Also, a 70-degree tilt with isometric FES resulted in a greater increase in heart rate than a 70-degree tilt without stimulation. Applying FES increased the blood pressures in the supine position by approximately 20 mmHg, compared to the blood pressures in the supine without FES. However, at a 70-degree tilt, systolic blood pressure with FES was still lower by approximately 15 mmHg, compared to the supine systolic pressure without FES.

In the study by Chao and Cheing [43], a 60-degree head-up tilt with isometric FES resulted in lower heart and higher blood pressures than a 60-degree tilt without stimulation. However, even with isometric FES, a 60-degree head-up tilt decreased systolic and diastolic blood pressures by approximately 10 mmHg, compared to the supine values with FES. Also, after a 60-dgeree head-up tilt with FES, heart rate increased by approximately 15%, compared to the supine value with FES. Although isometric FES reduced the increase in heart rate and decrease in blood pressures during a head-up tilt, the observations still suggested that the FES intervention was somewhat inadequate. In summary, the above studies largely demonstrated ineffectiveness of isometric FES in improving the cardiovascular response of individuals with SCI to increased orthostatic stress.

To the author’s knowledge, there have been two studies [3,4] that investigated the effects of dynamic FES, which is a combination of passive leg movements and FES. During dynamic FES, electrical stimulation is applied to the leg muscles, in synchronization with the passive movements. Similar to isometric FES, the FES-induced muscle contractions are intended to induce venous return. Thrasher et al. found that, compared to isometric FES, dynamic FES induced better cardiovascular responses to sustained upright posture at a 75-degree head-up tilt. In their study, six out of sixteen able-bodied participants experienced pre-syncope or syncope with isometric FES. However, with dynamic FES, these six participants were able to withstand 30 minutes of sustained upright posture without experiencing pre-syncope or syncope. Chi et al. found that, for ten able-bodied participants, dynamic FES induced the largest cross-sectional area of the inferior vena cava, which was a surrogate measure of venous return. Because the ability to induce venous return is compromised in individuals with SCI, dynamic FES has the potential to maintain their arterial pressure by maintaining venous return.

2.4 Intended Mechanism of Dynamic FES

During dynamic FES, the electrical stimulation and passive movements of the lower limbs are intended to induce venous return. Adequate venous return will maintain the arterial blood pressure and, consequently, cerebral perfusion.

2.4.1 Venous Pump

In addition to vasoconstriction, an important and effective mechanism that counteracts postural hypotension is skeletal muscle contraction in the lower limbs. Muscle contractions prevent venous pooling by compressing the deep and superficial veins in the lower extremities [5,44]. Because the veins have one-way valves, compressed veins propel the blood toward the heart against gravity [13]. This mechanism is known as the venous pump, and its effects have been demonstrated by several studies [44-46]. Unfortunately, the venous pump is usually severely impaired in individuals with SCI. During passive standing, the venous pressure in the lower extremities can reach their maximum value in approximately 30 seconds [5]. If this increase in venous pressure is not relieved by muscle contractions, the pressure drives the fluid out of the capillaries into tissue space, decreasing the blood volume [5,47]. The blood volume can decrease by 10 to 20% in 15 to 30 minutes [5].

2.4.2 Frank-Starling Mechanism

According to the Frank-Starling mechanism of the heart, cardiac output is determined by the amount of venous return [5]. Increased venous return (i.e., atrial filling) will proportionally increase the contractile force of the myocardium, within physiological limits [5]. In other words, within physiological limits, venous return equals cardiac output, and there is no accumulation of the blood in the heart. Because the Frank-Starling mechanism is based on the optimal overlap of myocardial fibers, it is independent of the sympathetic nervous system and unaffected by SCI.

2.4.3 Maintaining Cerebral Oxygenation under Orthostatic Stress

Ultimately, sufficient cerebral oxygenation must be maintained to prevent the symptoms of orthostatic hypotension [48,49]. In individuals with cervical and high-thoracic SCI, cerebral oxygenation is closely correlated with cerebral blood flow [50]. Therefore, maintaining cerebral perfusion should ensure sufficient oxygenation.

Normally, cerebral blood flow represents approximately 12 to 15% of cardiac output. This amounts to 50 to 60 ml of blood per 100 g of brain tissue per minute, satisfying the minimum requirement for cerebral oxygenation to maintain consciousness: approximately 3 to 3.5 ml of oxygen per 100 g of brain tissue per minute [8]. In a healthy individual, cerebral perfusion is well maintained when the mean arterial blood pressure is between 60 and 140 mmHg [5,8,49]. However, if the mean arterial pressure falls below 60 mmHg, cerebral blood flow is no longer regulated and will decrease significantly [5]. Despite strong sympathetic innervation of the brain, SCI has little effect on the regulation of cerebral blood flow [5]. Therefore, sufficient cerebral perfusion should be ensured by maintaining arterial pressure, which depends on cardiac output and systemic vascular resistance [5,8]. Considering the Frank-Starling mechanism, maintaining adequate venous return has obvious and significant importance in preventing the symptoms of orthostatic hypotension.

SCI has little effect on the cerebral blood flow because of its autoregulation. The autoregulation of cerebral perfusion is based on myogenic, metabolic, neurogenic, and endothelial mechanisms [49,51]. The myogenic mechanism responds to changes in the transmural pressure of the cerebral vasculature. When the pressure increases, vasoconstriction occurs to increase the vascular resistance, which maintains a steady volumetric flow [49,51]. The metabolic mechanism induces vasodilation or constriction in response to the chemical composition of the cerebral blood. For example, an increased plasma concentration of waste metabolites will induce vasodilation to clear them from cerebral circulation [49,51]. The neurogenic mechanism refers to the tonic vasoconstriction of the cerebral vasculature due to sympathetic stimulation [49,51]. The fourth mechanism is the tonic release of vasodilator substances by the cerebral endothelium [49,51].

2.4.4 Effect of Respiration on Systemic Venous Return

Respiration is known to interact with systemic venous return. During inspiration of diaphragmatic breathing, the descending diaphragm decreases the intrathoracic pressure, which promotes right atrial filling. However, the descent of the diaphragm also increases the abdominal pressure, which impedes venous return [45]. One study [45] investigated the effect of diaphragmatic breathing and rib cage breathing on venous return, which was induced by contracting calf muscles: one contraction per inspiration and expiration. During diaphragmatic breathing, venous return was reduced during inspiration and increased during expiration. This pattern of venous return was reversed for ribcage breathing, to an extent: venous return did not change significantly between inspiration and expiration of rib cage breathing. It is important to note that the two types of respiration had no net effect on venous return [45].

Chapter 3: Materials and Methods

3.1 Participants

3.1.1 Recruitment and Screening of Potential Participants

Potential participants were recruited via referrals and advertisement. Referrals were made by the collaborating healthcare professionals at the Lyndhurst Centre, Toronto Rehabilitation Institute, where all experiments were conducted. The study was also advertised at the Lyndhurst Centre, and potential participants contacted the investigators in response to the advertisement. All potential participants were screened for eligibility by their designated physiatrists. Also, the investigators were granted access to the potential participants' medical records to confirm their eligibility.

3.1.2 Inclusion and Exclusion Criteria

All participants met the following inclusion criteria:

- Male or pre-menopausal female
- Individuals from 18 to 60 years of age
- Individuals who were paraplegic or quadriplegic, with ASIA impairment scale of A, B, C, or D
- Individuals with SCI at or above T6 level
- Individuals whose spinal cord pathology was due to a distinct and sudden onset (less than 24 hours), rather than a prolonged onset; spinal cord injuries had traumatic or non-traumatic etiology

- Individuals who were neurologically stable (i.e., the endogenous response to the injury has stabilized)
- Individuals who were willing to undergo a 70-degree head-up tilting from the supine position
- Individuals who were willing to undergo FES of the leg muscles and imposed passive leg movements following the 70-degree head-up tilt
- Individuals whose tibialis anterior, calf, quadriceps, and hamstring muscles in both legs could be contracted using FES
- Individuals who were willing to undergo ultrasound scanning of the chest during a 70-degree head-up tilt
- Individuals who could understand instructions in English

Postmenopausal women were excluded from this study because of the significantly higher risk of cardiovascular and cerebrovascular disease: Cardiovascular and cerebrovascular disease account for 75 to 76% of deaths in postmenopausal women [52]. Similarly, cardiovascular disease account for more than 40% of deaths in individuals aged 65 and older [53]. Also, more than 80% of deaths from cardiovascular disease occur in individuals aged 65 and older [53]. Therefore, this study limited the age of participants at 60 and excluded postmenopausal women.

The American Spinal Injury Association Impairment Scale (AIS) is used by clinicians and researchers to classify and describe the effects of SCI [54,55]. AIS specifies that classification A corresponds to ‘No sensory or motor function is preserved in the sacral segment S4-S5’, classification B corresponds to ‘Sensory but not motor function is preserved below the neurological level and includes the sacral segment S4-S5’, classification C corresponds to ‘Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3’, classification D corresponds to ‘Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade greater than or equal to 3’, and classification E corresponds to ‘Sensory and motor functions is normal’ [55].

The restriction on the injury level ensured that a participant's sympathetic control of the systemic vasculature was significantly impaired. Without sympathetic vasoconstrictions, the effect of increased venous return from the applied passive movements and FES would be more pronounced.

All participants did not meet the exclusion criteria:

- Individuals who did not sign the informed consent form
- Individuals with poor understanding of the purposes of the study
- Individuals with brain injuries or current psychiatric illness
- Individuals who had experienced transient ischemic attack, stroke, or myocardial infarction prior to participating in the study
- Individuals with atrial or ventricular fibrillation
- Individuals with chronic renal failure
- Individuals with brittle diabetes
- Individuals with lower extremity peripheral nerve damage
- Individuals with current drug addiction
- Individuals with skin problems (e.g. skin injury, rash, scar, or pressure ulcer) at the location of stimulation electrode placement
- Individuals with deep vein thrombosis
- Individuals with untreated autonomic dysreflexia
- Individuals on alpha blockers or beta blockers
- Individuals who could not assume an upright, standing posture due to contractures
- Individuals with aortic aneurism (asymptomatic aortic aneurisms were screened by histories of abdominal or brain aneurysms)
- Individuals who had undergone coronary artery bypass surgery or lower extremity revascularization
- Individuals who experienced discomfort from involuntary contractions caused by electrical stimulation
- Individuals with non-consolidated fractures, unstable vertebral column, severe osteoporosis, or pseudarthrosis

3.2 Experimental Protocol

3.2.1 Ethics Approval

Prior to the experiments, the protocols for this study were approved by the Research Ethics Board of the Toronto Rehabilitation Institute, Canada. All participants gave written consent prior to participating in the study.

3.2.2 Environmental Conditions

The experiments were conducted during normal hospital hours, between 10 a.m. and 2 p.m. The room temperature was normal during all experiments.

3.2.3 Fasting and Dietary Restrictions

Prior to the experiment, the participants were instructed to refrain from consuming food, caffeine, nicotine, and alcohol for eight hours. The participants were also instructed to refrain from consuming fluid for two hours before the experiment.

The fasting requirement prevented unnecessary risk of hypotension caused by insulin. In individuals with compromised autonomic blood pressure regulation, an increased plasma concentration of insulin (e.g., following the ingestion of carbohydrate) decreases blood pressure [56]. The participants also refrained from consuming common psychoactive substances, which have transient effects on the cardiovascular system that could contaminate the results. The reasons for the dietary restrictions were the following:

- An increased plasma concentration of nicotine impairs arterial vasodilation, speeds up heart rate, and increases the cardiac output [57,58]. Consequently, nicotine causes transient hypertension [57,58].

- Alcohol increases the baseline heart rate and sympathetic nervous activity [59,60]. It also significantly impairs arterial vasoconstriction, thus increasing the risk of orthostatic hypotension [59].

- Consuming caffeine impairs a person's ability to maintain blood pressure under orthostatic stress, presumably from depressed baroreflex [61,62]. Caffeine also decreases the cerebral blood flow [63].

3.2.4 Management of Autonomic Dysreflexia

Autonomic dysreflexia (AD) is a clinical condition triggered by a stimulus below the level of injury and characterized by a sudden increase in the blood pressure, followed by compensatory bradycardia [7]. Other symptoms include headache, profuse sweating, contraction of the urinary bladder and large intestine, and penile erection and ejaculation [7]. Individuals with SCI above T6 are significantly more likely to experience AD [7,64]. Also, individuals with complete injuries are at greater risk. In one study [64], 91% of the participants with complete tetraplegia experienced AD, while only 27% of the participants with incomplete tetraplegia experienced AD [64]. The known stimuli that can cause AD include the distension of urinary bladders and bowels, cutaneous stimulation, pressure sores, FES, and passive leg movements [7].

In this study, the stimuli that may elicit autonomic dysreflexia (AD) included weight bearing, passive movements of the legs, FES, and pressure from the harness. If an onset of AD was suspected during the experiment, the investigators were instructed to immediately identify and remove the stimulus that caused AD. Also, all participants were advised to empty their bladder and bowel before the experiment to minimize the risk of AD due to bladder and bowel distension.

3.2.5 Overview of the Experimental Protocol

The experiment involved four test conditions, which were applied in a randomized sequence. Each test condition was applied for ten minutes while the participant was tilted head-up to 70 degrees from the supine position. While the participants were tilted, they were asked to report any symptoms of OH, such as dizziness or lightheadedness. During the last one minute of each test condition, the cross-section of the inferior vena cava was recorded in the transverse plane using an ultrasound system. After each condition, the participant was tilted back to the supine position and rested for ten minutes. Throughout the experiment, the beat-to-beat blood pressure was recorded non-invasively. When the test condition did not involve FES, the EMG activities of the leg muscles were recorded. Each experiment lasted for approximately three hours.

3.2.6 Outline of the Experimental Protocol

The experiment was divided into three phases: preparation, data collection, and discharge.

3.2.6.1 Preparation

First, the EMG and FES electrode were placed on the participant. The FES electrodes were placed to stimulate the tibialis anterior, calf, quadriceps, and hamstring muscles of both legs. The EMG electrodes were placed over the bellies of the tibialis anterior, medial gastrocnemius, rectus femoris, and biceps femoris muscles of both legs. All electrodes were secured with, double-sided adhesive tapes, surgical tapes, and self-adhesive bandage.

Once the electrodes were securely in place, the investigators measured the threshold and maximum amplitudes for the electrical stimulation of each muscle. The threshold amplitude was defined as the amplitude at which the first detectible contraction occurred. The contraction was detected either visually or through touch. The maximum amplitude was defined as either the minimum amplitude required to achieve maximum contraction or the maximum tolerable amplitude (for participants with sensory incomplete SCI). During data collection, each muscle was stimulated at 70% of the maximum amplitude, which was above the threshold in most cases. If 70% of the maximum amplitude was below the threshold, the threshold was used for stimulation instead.

Finally, the participant was safely transferred onto the tilt table and securely harnessed. Then, the finger cuff of the cardiovascular monitor was attached to the right middle finger. Once the monitor started recording, the participant was instructed to relax and breathe normally. The cardiovascular parameters were recorded without interruption until the end of data collection. In the supine position, the participant rested for 10 minutes to stabilize the cardiovascular parameters.

3.2.6.2 Data collection

After the first supine rest, the participant underwent four test conditions in a random order. Each condition lasted for 10 minutes under a 70-degree head-up tilt, and each condition was followed by 10 minutes of supine rest. The supine rest re-stabilized the cardiovascular state of the participant.

The four test conditions were applied under a 70-degree head-up tilt: 1) no intervention, 2) imposed passive movements of the lower extremities, 3) isometric FES of the lower extremity muscles, and 4) a combination of passive movements and FES of the lower extremity muscles. In this document, the last condition (combination of passive movements and FES) is referred to as dynamic FES. During the last one minute of each test condition, the cross-section of the inferior vena cava was recorded in the transverse plane. The tilt angle of 70 degrees was chosen to comply with the definition of orthostatic hypotension by the American Autonomic Society and American Academy of Neurology [16] and to observe significant cardiovascular response to orthostatic stress [65]. The participants were asked to report any symptoms of OH, such as dizziness or lightheadedness.

3.2.6.3 Discharge

After the last supine rest (following the fourth test condition), the harness and all electrodes were removed from the participant, and the participant was transferred safely to a wheelchair.

3.3 Functional Electrical Stimulation Protocols

Both isometric and dynamic FES used a pulse width of 300 μs and frequency of 40 Hz, which were comparable to other studies that used FES to prevent OH [3,42,43]. The stimulation waveforms were asymmetric biphasic to prevent tissue damage from the delivered electrical stimulus [38,39].

3.3.1 Protocol for Isometric Functional Electrical Stimulation

Figure 1 shows the stimulation pattern for isometric FES. The dashed line represents the stimulation of the tibialis anterior and calf muscles, whereas the solid line represents the stimulation of the quadriceps and hamstring muscles. The two stimulation waveforms are identical, but they had 1.2 seconds of offset. Both waveforms first ramped up their pulse duration over 0.3 seconds. Then, the pulse duration was held constant for 0.9 seconds, before it ramped down over 0.3 seconds. The waveforms shown Figure 1 were repeated for the duration of the isometric FES intervention. Thus, the alternating stimulation between the shank and thigh generated rhythmic contractions, which mimicked a squeezing motion that induced venous return. The stimulation was symmetrical between the two legs. This stimulation pattern have been used in previous studies on isometric FES [40-43].

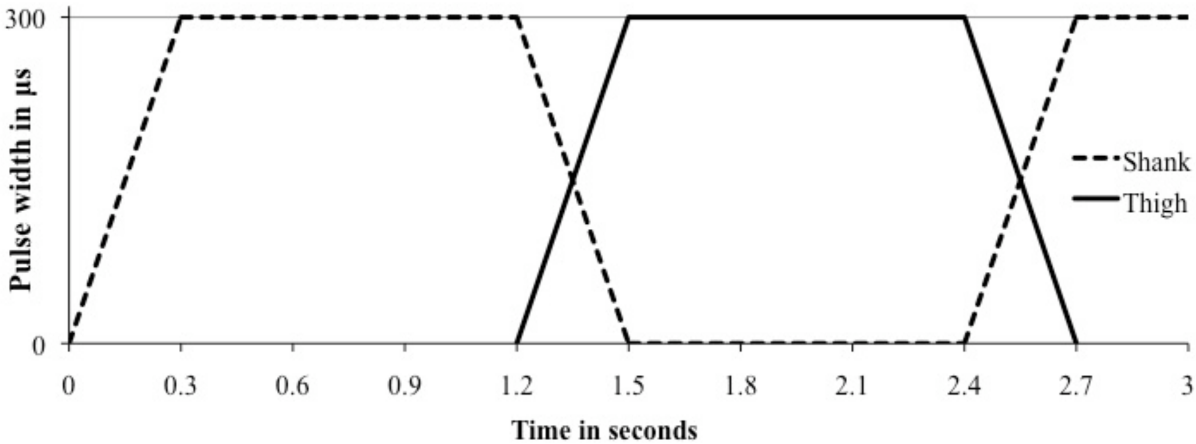

Figure 1: The stimulation pattern for the isometric FES intervention. The two complete waveforms comprise one cycle of stimulation. The cycle was repeated for the entire duration of the isometric FES intervention. The dashed line represents the stimulation of the tibialis anterior and calf muscles, and the solid line represents the stimulation of the quadriceps and hamstring muscles. The stimulation was symmetrical between the two legs.

3.3.2 Protocol for Dynamic Functional Electrical Stimulation

During dynamic FES, the muscles were stimulated in synchronization with the imposed passive movements. Specifically, each muscle was stimulated when it was shortening. Because the muscle lengths change differently during different multi-joint movements, the passive movement on the tilt table was simulated. The simulation allowed the investigators to determine how the muscle lengths changed during the experiment.

3.3.2.1 Regression Equation of Muscle Lengths during Multi-joint Movements

To determine the lengths of leg muscles during a multi-joint movement, the following regression equation was used:

$$L = C_0 + C_1\alpha + C_2\beta + C_3\beta^2 + C_4\phi,$$

where L is the normalized length of a lower extremity muscle; C_0, C_1, C_2, C_3, and C_4 are regression coefficients, whose values differ for each muscle; and α, β, and ϕ are the hip, knee, and ankle angles, respectively [1]. In the above equation, the length of each muscle was normalized to either the thigh or shank length, whichever limb segment a particular muscle was mostly located on. For example, the length of tibialis anterior would be normalized to the shank length, whereas the length of biceps femoris would be normalized to the thigh length. The equation was derived from computer simulations of multi-joint movements of the lower extremities in the sagittal plane. The simulations used anthropometric data of adult participants, as well as muscle origin and insertion locations in cadavers. The simulations estimated the lengths of leg muscles for different combinations of joint angles (see Figure 2), and the results were used to derive the above equation through regression.

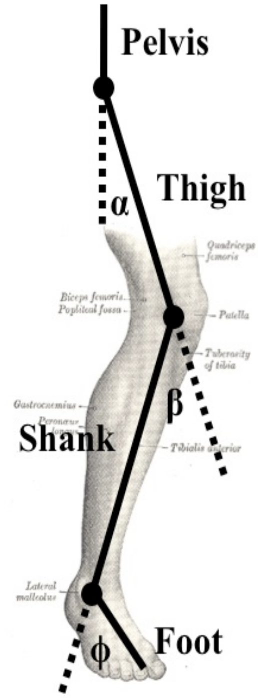

Figure 2: The definitions of joint angles used by Hawkins and Hull [1]**. The hip angle (**α**) is between the pelvis and thigh, the knee angle (**β**) is between the thigh and shank, and the ankle angle (**ϕ**) is between the shank and foot. The dotted lines represent the imaginary extensions of the limb segments. The original anatomical image was taken from the work of Gray** [2]**.**

3.3.2.2 Linked-segment Model of Lower Extremity

To determine the hip, knee, and ankle angles during a multi-joint movement, a lower extremity was modeled as a multi-link structure in a commercial simulation environment (Simulink Version 7.4 and SimMechanics Version 3.1.1, The MathWorks, Inc., USA). The foot, shank, and thigh were each represented as a rigid body. The three rigid bodies were connected to each other via revolute joints, which simulated the rotational degree of freedom at the ankle, knee, and hip joints in the sagittal plane. The toe of the foot link was connected to the inertial reference via a revolute joint, while the proximal end of the thigh link was also connected to the reference via a revolute joint. These constraints were implemented to match the simulated and actual kinematics of the leg movements on the tilt table. Figure 3 shows the geometrical representation of the lower extremity, and Figure 4 shows the block diagram used for simulation.

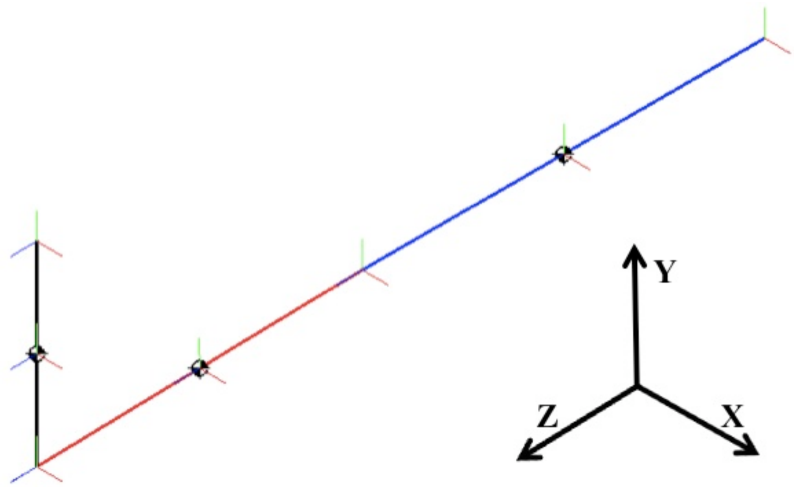

Figure 3: The isometric view of the geometrical representation of a lower extremity in a commercial simulation environment. The links representing the foot, shank, and thigh are colored as black, red, and blue, respectively. The y-axis of the inertial reference frame points against the direction of the gravitation acceleration, and the z-axis points along the long bones of the leg and toward the ankle.

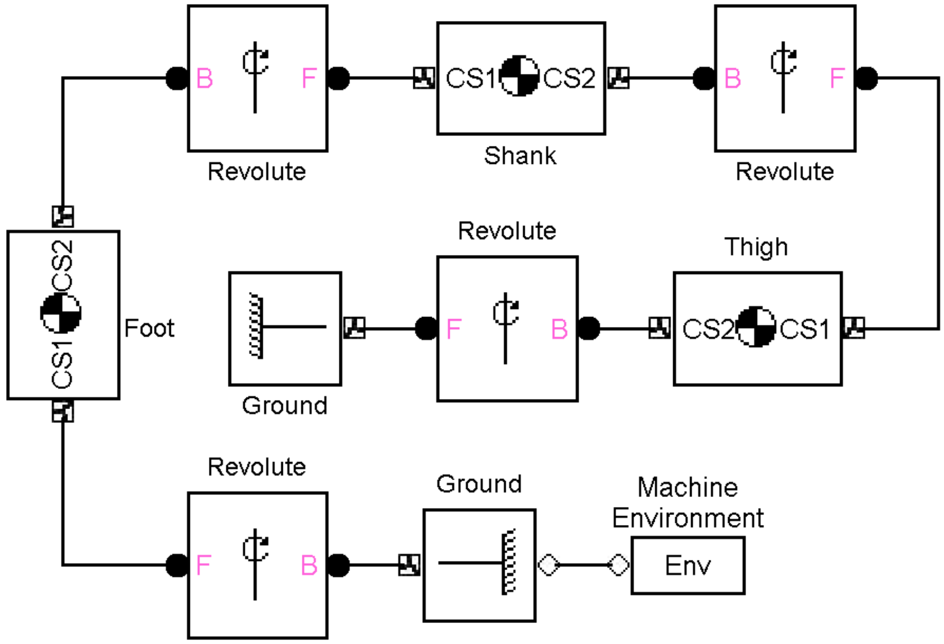

Figure 4: The block diagram of a lower extremity, as implemented in a commercial simulation environment. Each revolute joint represents a rotational degree of freedom in the sagittal plane. The toe of the foot link and the proximal end of the thigh link were connected to the inertial reference (ground) via a revolute joint.

Although not shown in Figure 4, the revolute joint at the proximal end of the thigh link was connected to a joint actuator, which rotated the thigh link with a sinusoidal signal (see Figure 5). The simulation involved one cycle of hip flexion and extension, between the hip angles of 6 and 26 degrees. The hip angle was defined as the angle from the horizontal to the thigh link (see Figure 6). The stimulation used the same range and speed of motion as the actual kinematics in the experiments. The output of the simulation was the hip, knee, and ankle angles during the simulated movement.

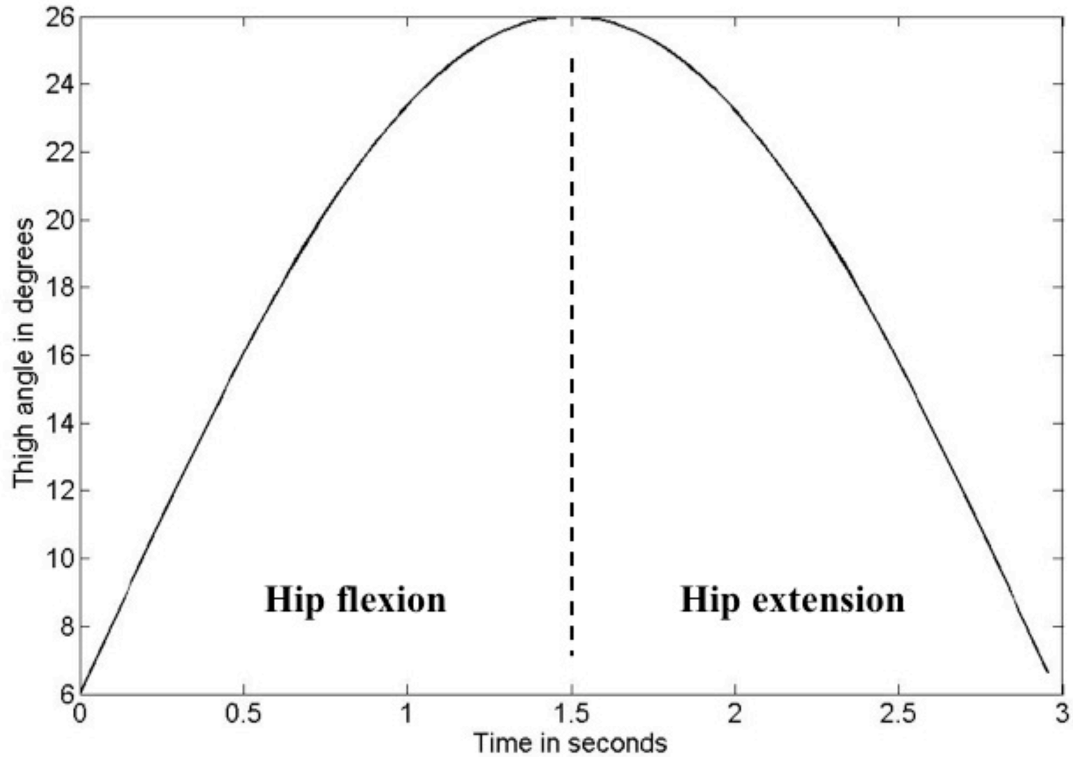

Figure 5: Sinusoidal input for the thigh angle. The same range (6 to 26 degrees) and speed (40 steps per minute) of motion as those used in the experimental protocol.

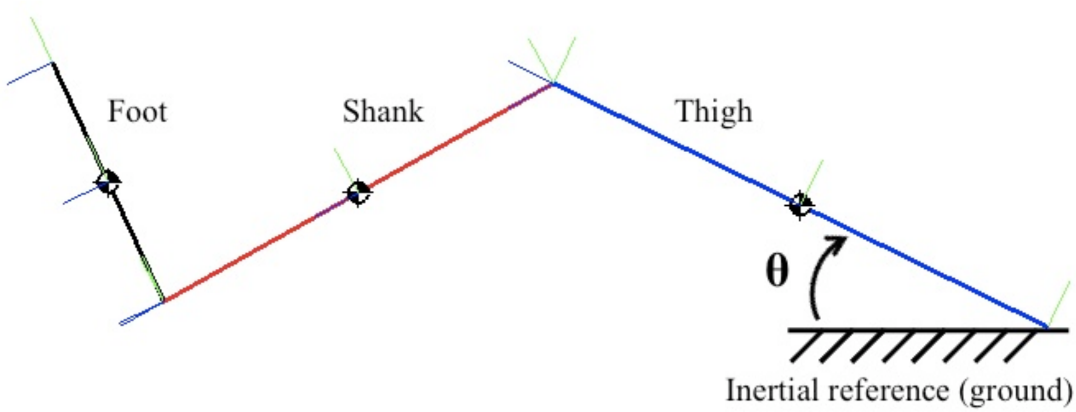

Figure 6: The linked-segment model of the leg, as implemented in a commercial simulation environment. The thigh angle (labeled as θ) was defined as the angle from the horizontal to the thigh link.

3.3.2.3 Calculated Muscle Lengths during Multi-joint Movement

The calculated joint angles were used in the regression equation to calculate the lengths of lower extremity muscles during the simulated multi-joint motion.

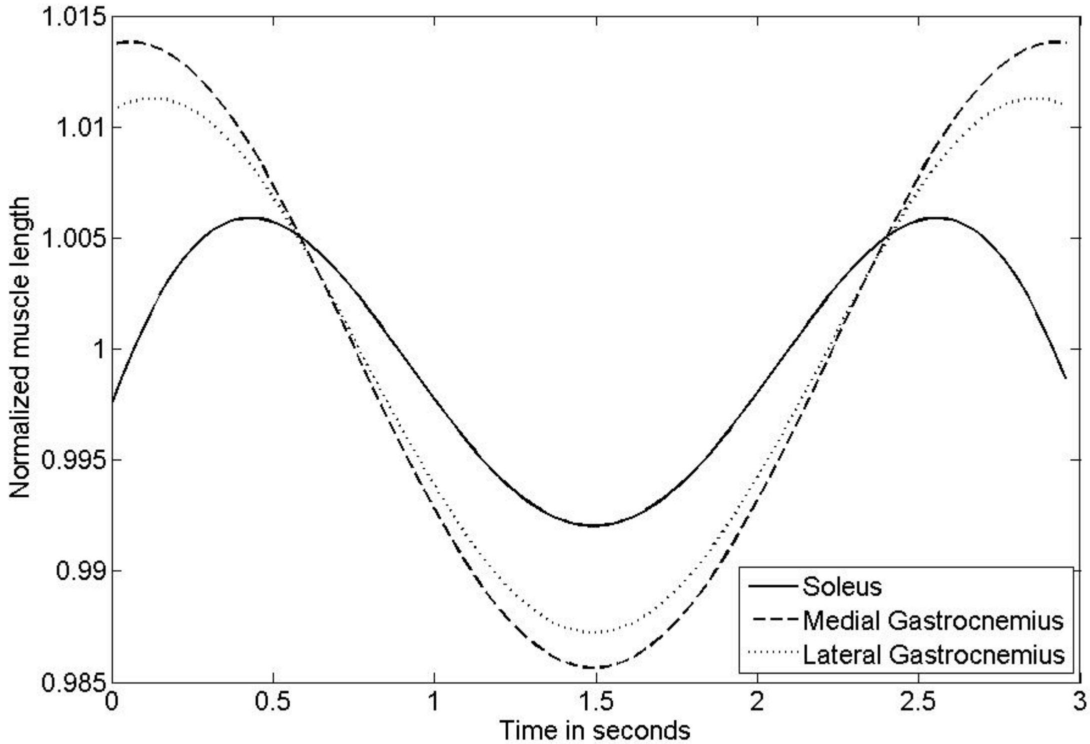

Figure 7: Calculated lengths of calf muscles during one cycle of hip flexion and extension. Each muscle length has been normalized to its average length during the simulated motion. The first 1.5 seconds corresponds to hip flexion, followed by 1.5 seconds of hip extension.

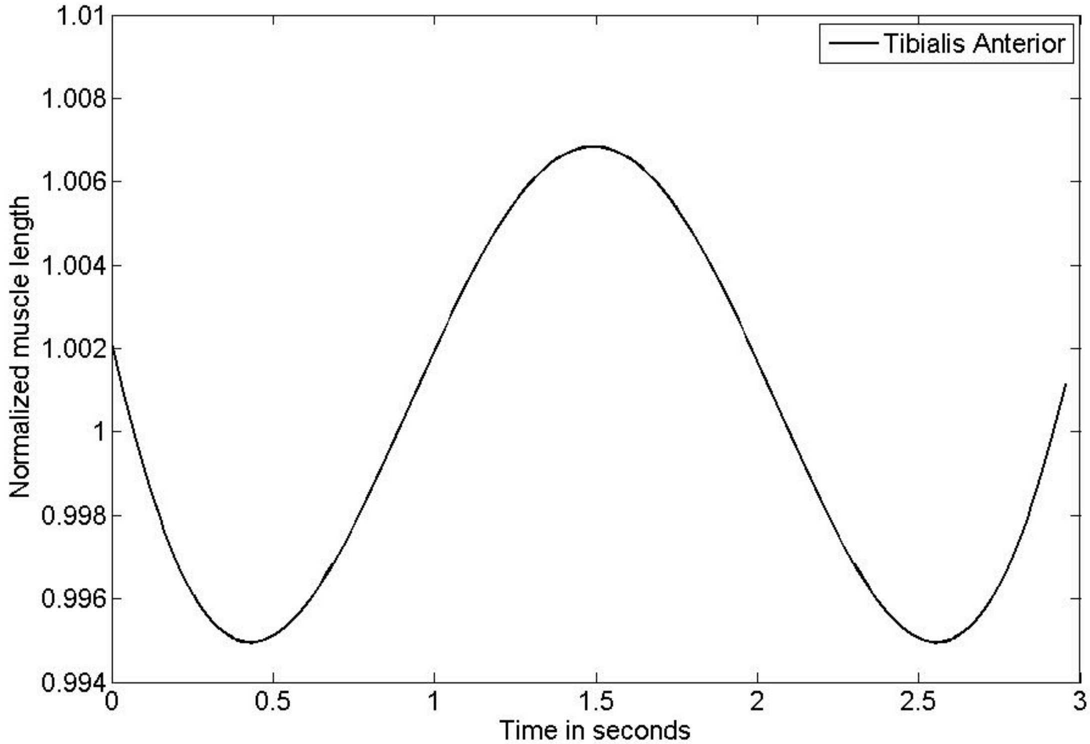

Figure 8: Calculated length of tibialis anterior during one cycle of hip flexion and extension. The muscle length has been normalized to its average length during the simulated motion. The first 1.5 seconds corresponds to hip flexion, followed by 1.5 seconds of hip extension.

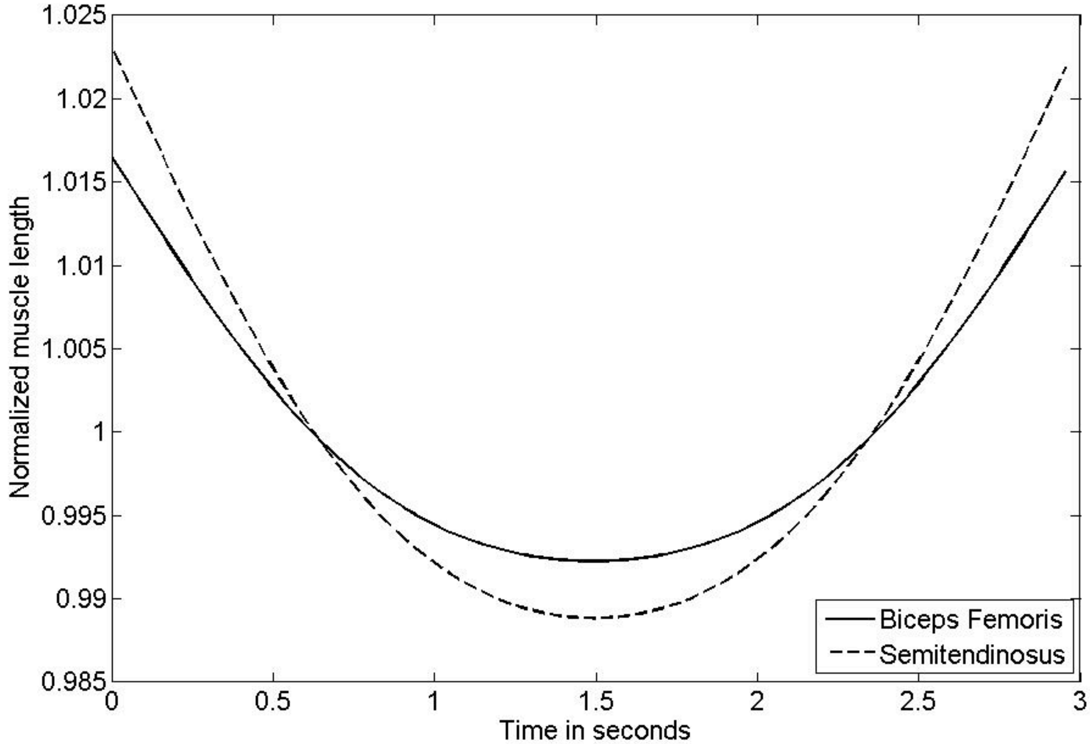

Figure 9: Calculated lengths of hamstring muscles during one cycle of hip flexion and extension. Each muscle length has been normalized to its average length during the simulated motion. The first 1.5 seconds corresponds to hip flexion, followed by 1.5 seconds of hip extension.

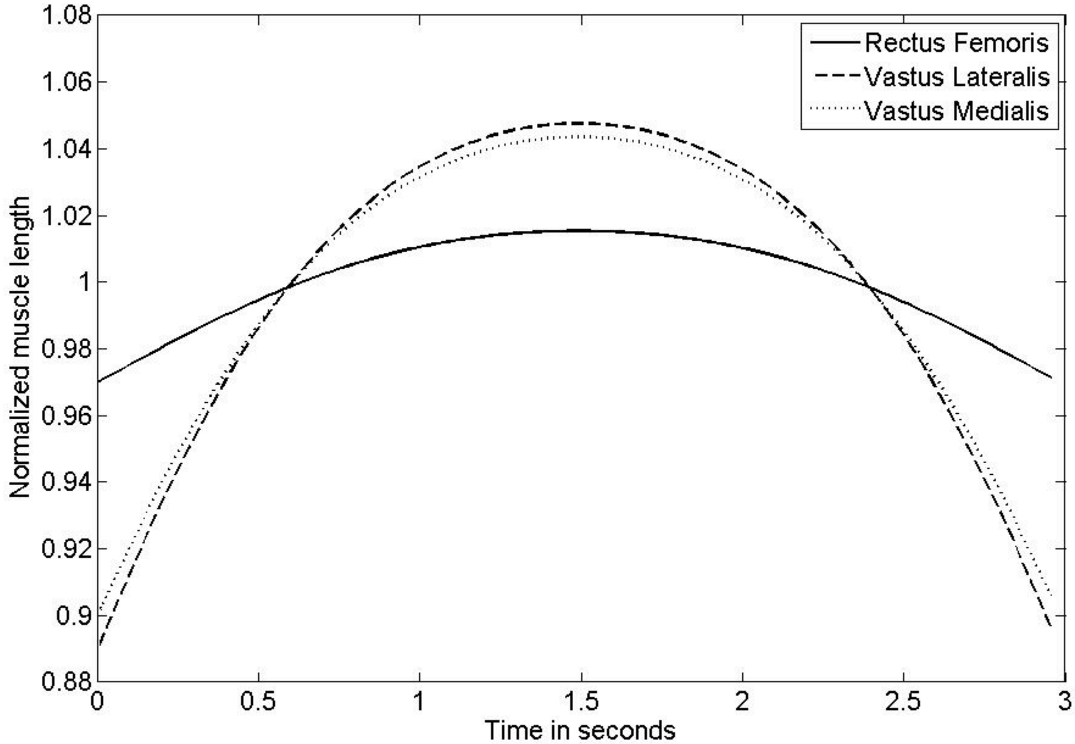

Figure 10: Calculated lengths of quadriceps muscles during one cycle of hip flexion and extension. Each muscle length has been normalized to its average length during the simulated motion. The first 1.5 seconds corresponds to hip flexion, followed by 1.5 seconds of hip extension.

3.3.2.4 Stimulation Pattern for Dynamic FES

Figure 7 through Figure 10 show consistent patterns for each muscle group. The calf and hamstring muscles shorten during hip flexion, whereas the tibialis anterior and quadriceps muscles shorten during hip extension. During dynamic FES, each muscle group was stimulated while its muscles were shortening (see Figure 11). Therefore, the tibialis anterior and quadriceps muscles were stimulated during hip extension, and the calf and hamstring muscles were stimulated during hip flexion. The same waveform as isometric FES was used for dynamic FES. As shown in Figure 11, stimulation is not applied while the leg muscles are lengthening. This is because the FES-induced contractions should not oppose the lengthening of the leg muscles during passive movements. Stimulating a muscle only while it is shortening generated more physiologically natural contractions.

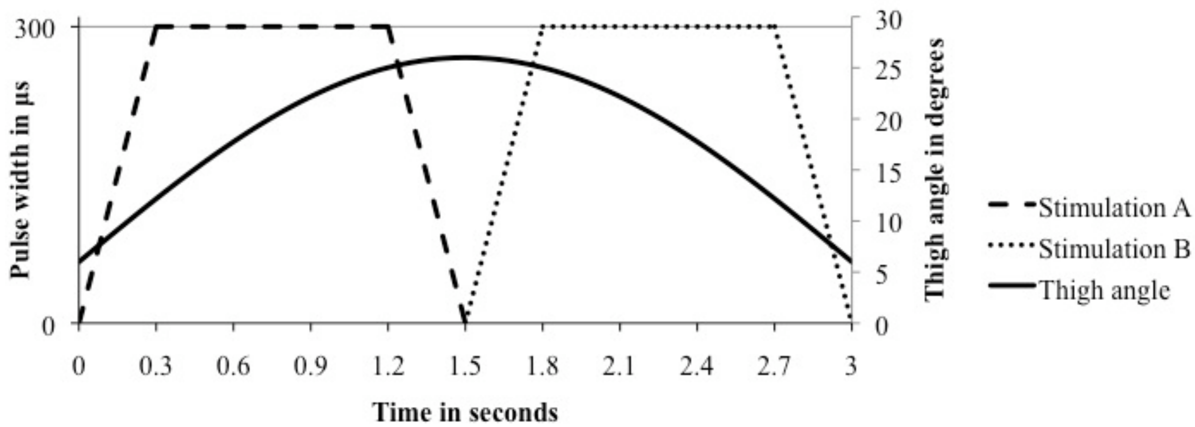

Figure 11: One cycle of stimulation for dynamic FES. The first 1.5 seconds corresponds to hip flexion, followed by 1.5 seconds of hip extension. This cycle was repeated for the duration of dynamic FES. The dashed line represents the stimulation pattern for the calf and hamstring muscles. The dotted line represents the stimulation pattern for the tibialis anterior and quadriceps muscles.

3.4 Apparatus

3.4.1 Functional Electrical Stimulator

To apply FES, the investigators used two programmable transcutaneous FES systems (Compex Motion, Compex SA, Switzerland). The stimulator could apply stimulation with a frequency between 0 and 100 Hz, amplitude between 1 and 120 mA, and pulse width between 0 and 16000 µs [66].

These stimulators were current-regulated. Compared to voltage-regulated stimulators, current-regulated ones generate more consistent and repeatable muscle contractions by delivering a constant charge, regardless of the variable impedance between the electrodes and the motor neurons [38].

3.4.1.1 Electrode Placements

Each stimulator had four channels, which were connected to the tibialis anterior, calf, quadriceps, and hamstring muscles of one leg via surface electrodes (ValueTrode®, Axelgaard Manufacturing Co., Ltd., USA).

The investigators used 5cm×5cm rectangular electrodes on the tibialis anterior, and 5cm×9cm rectangular electrodes on the other muscle groups (see Figure 12). Each electrode was applied with conductive gel and secured with surgical tapes.

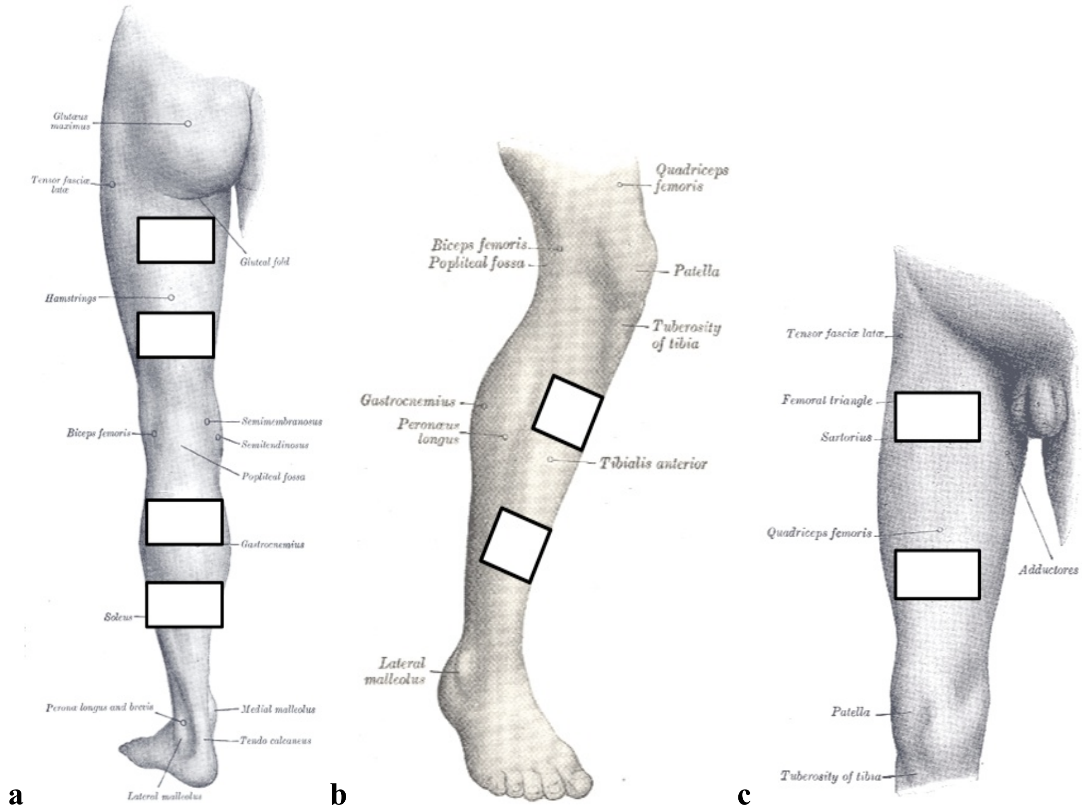

Figure 12: Approximate placements of the FES electrodes on (a) hamstring and calf muscles; (b) tibialis anterior; and (c) quadriceps muscles. White rectangles with solid lines represent the surface electrodes. The original anatomical images have been obtained from [2]**.**

3.4.2 Electromyography

This study monitored the EMG activities of medial gastrocnemius, tibialis anterior, biceps femoris, and rectus femoris during passive movements. If significant EMG activities are present during data collection, their effect must be considered during analysis. For example, if EMG activities occurred out of phase with FES, this would indicate that the leg muscles experienced constant contraction throughout the test condition. Consequently, the lack of relaxation (i.e., refilling of the lower extremity veins) may result in reduced venous return. Contrarily, if significant EMG activities coincide with the electrical stimulation, this may result in greater venous return.

To record the electromyograms of the leg muscles, the investigators used an eight-channel EMG measurement system (Bagnoli™ Desktop EMG System, Delsys Inc., USA). Before placing the EMG electrodes, the participant's skin was prepared to reduce the impedance of the skin. First, hair was removed from where the electrodes would be placed using a razor. Then, abrasion was lightly applied to remove the dead skin, and the skin was cleansed using alcohol wipes.

Surface electrodes were placed over the bellies of tibialis anterior, medial gastrocnemius, rectus femoris, and biceps femoris of both legs. The electrodes were fixed in place with thin double-sided adhesive tapes. Each electrode had two horizontal 99.9% silver bars, which were 10 mm in length, 1 mm in diameter, and 10 mm apart. The electrodes were placed so that the horizontal bars were perpendicular to the direction of each muscle. The reference electrode was placed over the lateral condyle of the left femur.

The output of EMG electrodes were amplified by a factor of 1000 and captured using a data acquisition system (PowerLab/12SP, ADInstruments, Australia) with a user-interface software (Chart v5.5.6., ADInstruments, Australia). The sampling frequency was 2 kHz. The data acquisition system also recorded a sinusoidal signal from the tilt table. This signal corresponded to the right hip angle and was used for the post processing of the electromyograms.

3.4.3 Tilt Table

This study used a novel tilt table with motorized stepping function (Erigo®, Hocoma AG, Switzerland). Using the graphical user interface of the tilt table, the investigators could control the degree of tilt, rate of passive leg movements, and the range of motion. The passive leg movements were generated by the motorized leg drives, whose cuffs fastened around the participant's thighs (see Figure 13).

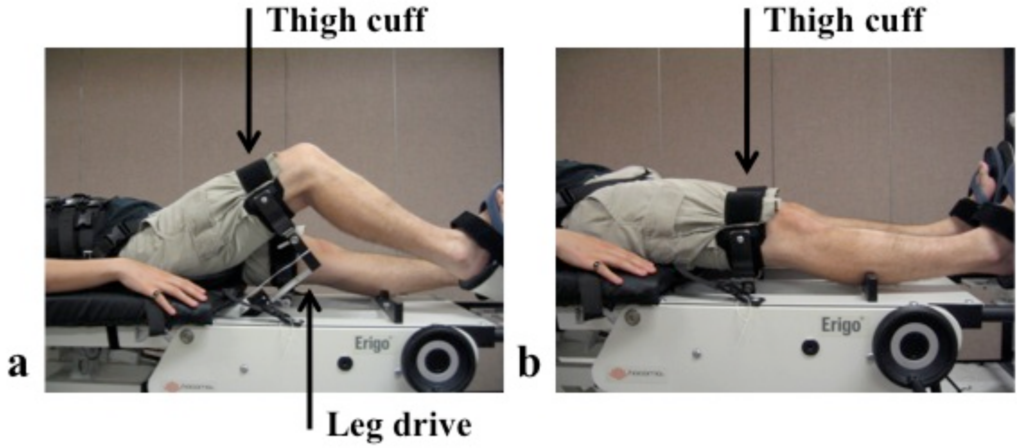

Figure 13: The mechanism of imposed passive leg movements on the tilt table. The figure shows the positions of the leg drive during hip flexion (a) and hip extension (b).

The leg drives rotated about an axis near the hip. Their rotational motion caused hip flexion and extension, while the knee and ankle joints also rotated in response. The participant’s feet were fixed to the foot plates, which rotated about an axis near the toe (see Figure 14).

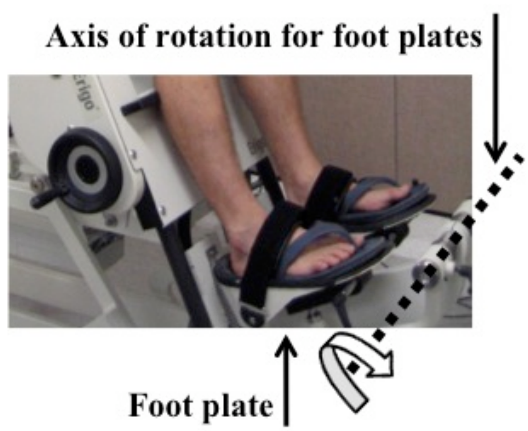

Figure 14: Foot plates and their axis of rotation.

For this study, the range of motion was 20 degrees, and the rate of stepping was 40 steps per minute (i.e., 40 hip flexions and 40 hip extensions in one minute). This rate ensured that there was at least one passive step during every inspiration and expiration [67], thus counteracting the effect of respiration on venous return.

3.4.3.1 Theories behind the Tilt Table's Design and Application

In individuals with SCI, the leg muscles can exhibit EMG activities during passive movements of the lower extremities [68-70]. The observed EMG activities are rhythmic, and their timing correlates with the rhythm of the passive movements. Although the activities are mainly observed when a muscle is mechanically stretched, a stretch reflex is probably not the primarily responsible mechanism. The general consensus postulates that the proprioceptive input from leg joints and loading of the soles excite the neural pathways that control locomotion (i.e., the central pattern generator) [5,69,71]. The tilt table used in this study was developed from this theory.

The tilt table has been developed to assist gait rehabilitation in the acute phase of SCI or other neurological disorders that affect gait [31]. The tilt table is designed to activate the central pattern generator by applying passive extension and flexion of the hip joint and loading of the soles [31,32]. One study has suggested that, in healthy individuals, passive leg movements on this tilt table activate the cortical regions classically associated with gait [72]. When activated, the central pattern generator will induce rhythmic contractions of the leg muscles.

With sufficient contractions, the tilt table can also be used to improve the cardiovascular response of individuals with SCI to head-up tilting. During the tilt, individuals with SCI are subjected to increased orthostatic stress, while the rhythmic contractions of the leg muscles will promote venous return to maintain the blood pressure. One study [31] demonstrated that passive movements at 30 steps per minute on this tilt table could maintain the blood pressure in individuals with cervical SCI for 30 minutes, under orthostatic pressure at a 60-degree tilt.

3.4.3.2 Effects of Wearing a Harness on Cardiovascular Response to Tilt

Figure 15 shows the harness worn by participants during data collection. One study [73] has investigated the effect of wearing a harness (very similar in design to the harness used in this study) on the cardiovascular response during postural change from supine to upright. The study found that the harness could not maintain blood pressure in individuals with cervical SCI during postural change. Wearing a harness increased the diastolic blood pressure by approximately 20% for individuals with thoracic SCI (between T2 and T6). However, the study did not provide the change in diastolic blood pressure without the harness for the same group of individuals with thoracic injuries. Wearing a harness also increased the systolic blood pressure for individuals with thoracic injuries, but the change was insignificant. Regardless of the injury level, the harness did not prevent postural tachycardia.

Figure 15: A harnessed participant under 70-degree head-up tilt.

3.4.4 Cardiovascular Monitoring System

During OH, cerebral hypoperfusion will lead to cerebral hypoxia, which causes the symptoms of OH (e.g., dizziness, lightheadedness, and fainting). These symptoms are what make upright standing postures intolerable for individuals with SCI. Cerebral blood flow and oxygenation can be measured non-invasively and continuously via near-infrared spectroscopy [74-76]. However, near-infrared spectroscopy only allows measurement in the surface brain tissue, approximately 2 cm deep or less [74,75]. Transcranial Doppler measures cerebral blood flow non-invasively and continuously [77,78]. However, Doppler ultrasonography measures the velocity of blood flow, not the volumetric flow rate, and it does not measure cerebral oxygenation.

Measuring cerebral blood flow and cerebral oxygenation would have directly indicated the effects of applied conditions. However, the investigators did not have access to these measurement systems. Also, given the strong maintenance of cerebral blood flow above the arterial pressure of 60 mmHg, the maintenance of arterial pressure should reliably indicate normal cerebral blood flow.

There are invasive and non-invasive methods of monitoring blood pressure. Classic non-invasive methods include the auscultatory method and the oscillometric method, both of which use an inflatable cuff on the upper arm. The auscultatory method determines the systolic and diastolic pressures by listening to the beginning and cessation of the Korotkoff sounds during the deflation of the cuff, whereas the oscillometric method approximates the systolic and diastolic pressures from the beginning and cessation of the pressure oscillation during the cuff deflation [79]. These non-invasive methods only provide a momentary value of the blood pressure, rather than beat-to-beat measurements [79]. Contrarily, invasive methods, such as arterial cannulation, central venous cannulation, and pulmonary artery catheterization, can provide beat-to-beat measurements of the blood pressure. However, they are associated with risks of thrombosis, embolism, infections, and nerve damage [80,81]. The cardiovascular monitoring system used in this study was non-invasive, provided beat-to-beat measurements, and was equipped with algorithms that estimated cardiovascular parameters other than blood pressures (Nexfin, BMEYE B.V., The Netherlands). The system consisted of a finger cuff (sensor), heart reference system, wrist unit, and monitor. The cuff was placed on the intermediate phalanx bone of the right middle finger. The heart reference system was used to account for the hydrostatic pressure difference between the heart and the finger cuff. Both the cuff and the heart reference system were connected to the wrist unit, which connected to the monitor.

To monitor the beat-to-beat cardiovascular parameters, the system uses two technologies: the volume-clamp method by Peñáz [82,83] and the physiologic calibration algorithm by Wesseling [84-86]. These technologies have been validated fairly well [84,86-88]. The volume-clamp method uses a finger cuff with a pneumatic balloon and an optical plethysmograph. The pressure applied by the balloon on the finger changes quickly, such that the transmural arterial pressure in the finger remains zero [85,86]. While the transmural pressure is zero, the 'unloaded' volume of an artery is measured by the optical plethysmograph. This volume is used as feedback for the physiologic calibration algorithm, which determines the instantaneous balloon pressure [85,86]. In short, the volume-clamp method and calibration algorithm comprise a closed-loop control system. Because the balloon pressure is adjusted to equal the finger arterial pressure, its waveform can be used to reconstruct the brachial arterial pressure [85,86].

3.4.5 Ultrasound System

To image the inferior vena cava in the transverse plane, the investigators used a diagnostic ultrasound system (ACUSON X150 ultrasound system, Siemens AG, Germany) with an abdominal transducer (CH5-2, Siemens AG, Germany), which had a frequency range of 2 to 5 MHz. The video output of the ultrasound machine was recorded directly onto the hard drive of a desktop computer via a video capture device (Dazzle Video Creator Plus HD, Pinnacle Systems, CA, USA).

To image the inferior vena cava in the transverse plane, the transducer was placed on the subcostal area of the chest, approximately 2 cm inferior to the xiphoid process of the sternum. In this position, the transducer imaged the inferior vena cava behind the liver. Similar methods have been used in other studies [89,90]. Ultrasound imaging was performed in the 2D-mode at 5 MHz. The same investigator performed the imaging for all participants.

The cross-sectional area of the inferior vena cava (IVC) was used as a surrogate for venous return. Due to the distensibility of the IVC, the cross-sectional area was assumed to change in proportion to the venous volumetric flow. Also, there is a strong correlation between the diameter of the IVC and central venous pressure [91,92], which increases with increased blood flow into the right atrium [5]. Using the cross-sectional area of the IVC as a surrogate for venous return is somewhat flawed: a diameter does not accurately represent the cross-sectional area of a distensible vein. However, the assumption was still used due to the lack of alternative measurements.

3.5 Post Processing

3.5.1 Ultrasound Images

All ultrasound videos were converted into an image sequence at 25 frames per second. The image sequences were then analyzed using image-processing software (ImageJ, National Institute of Health, USA). Only one investigator analyzed the images. A ‘blinded’ investigator, who did not know which image sequence corresponded to which test condition, manually selected the boundary of the inferior vena cava on each image (see Figure 16). Based on the selected boundary, the software calculated the cross-sectional area of the inferior vena cava. If the quality of an image was too poor to identify the boundary, the cross-sectional area was estimated using linear interpolation.

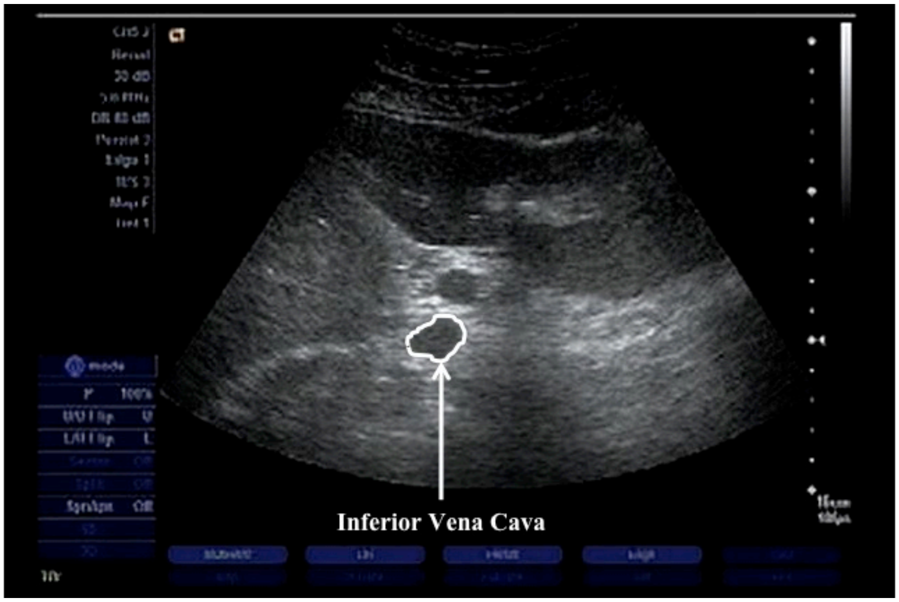

Figure 16: An ultrasound image of the inferior vena cava in the transverse plane. The boundary of the inferior vena cava is traced with a white line and indicated by an arrowhead.

Initially, the boundary of the inferior vena cava (IVC) was going to be selected using image analysis software (CellProfiler, Whitehead Institute for Biomedical Research and Massachusetts Institute of Technology, USA). The software would allow automated isolation of the region of interest and selection of the IVC in each image. However, the resolution of obtained ultrasound images was not sufficient to accurately discriminate the boundaries of the IVC. Thus, the investigators resorted to manual selection by a trained individual.

3.5.1.1 Sensitivity Analysis

The conversion rate of 25 frames per second yielded 1500 images for each minute of ultrasound recording. With four recordings (for four test conditions) per participant, analysis would be too labor intensive. Therefore, the number of analyzed images had to be minimized without compromising the outcome of the analysis. To determine the appropriate number of analyzed images, sensitivity analysis was performed, with sampling frequency and the length of an analyzed image sequence as variables. To perform the sensitivity analysis, three segments were sampled from each recording of one participant: Segment A contained the first 300 frames, Segment B contained 300 frames about the half-length point (30 seconds or 750th frame), and Segment C contained the last 300 frames.

First, the length of each segment was reduced by increments of 50 frames. Figure 17 through Figure 19 show the effect of reducing the length of each segment.

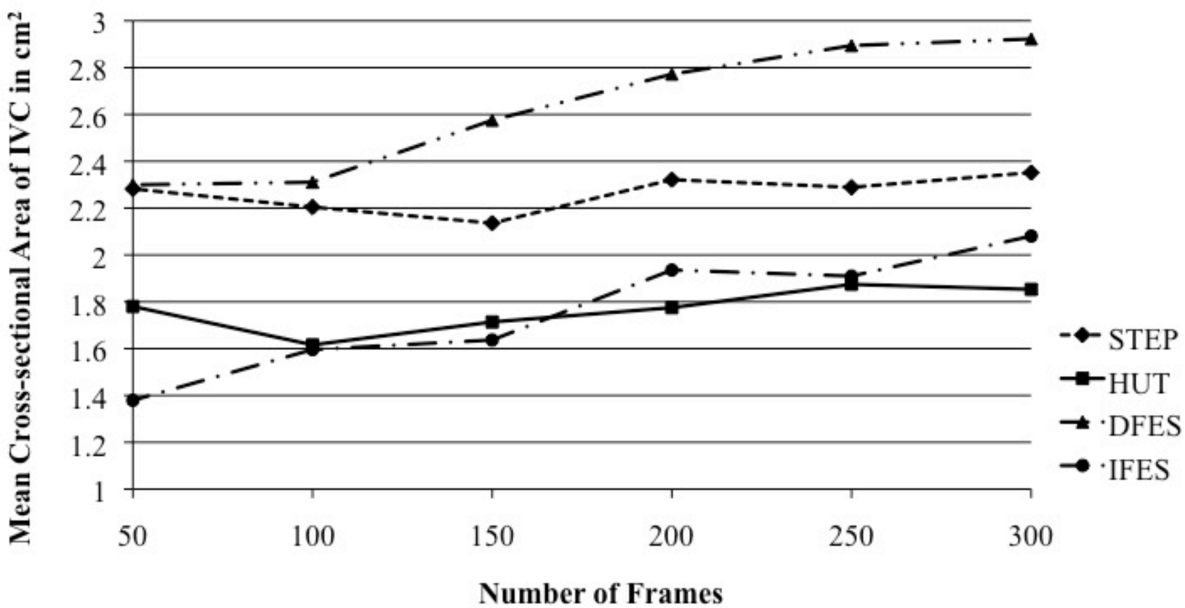

Figure 17: Mean cross-sectional area of the inferior vena cava (IVC) for Segment A. STEP represents imposed passive leg movements, HUT represents head-up tilt without intervention, DFES represents dynamic FES, and IFES represents isometric FES.

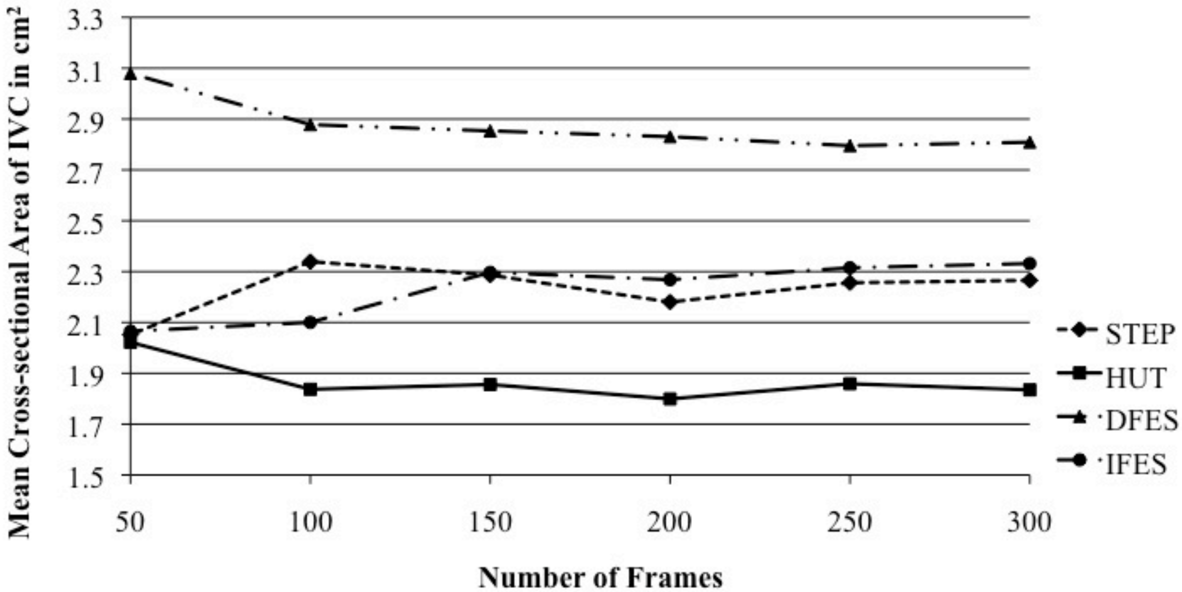

Figure 18: Measured mean cross-sectional area of the inferior vena cava (IVC) for Segment B. STEP represents imposed passive leg movements, HUT represents head-up tilt without intervention, DFES represents dynamic FES, and IFES represents isometric FES.

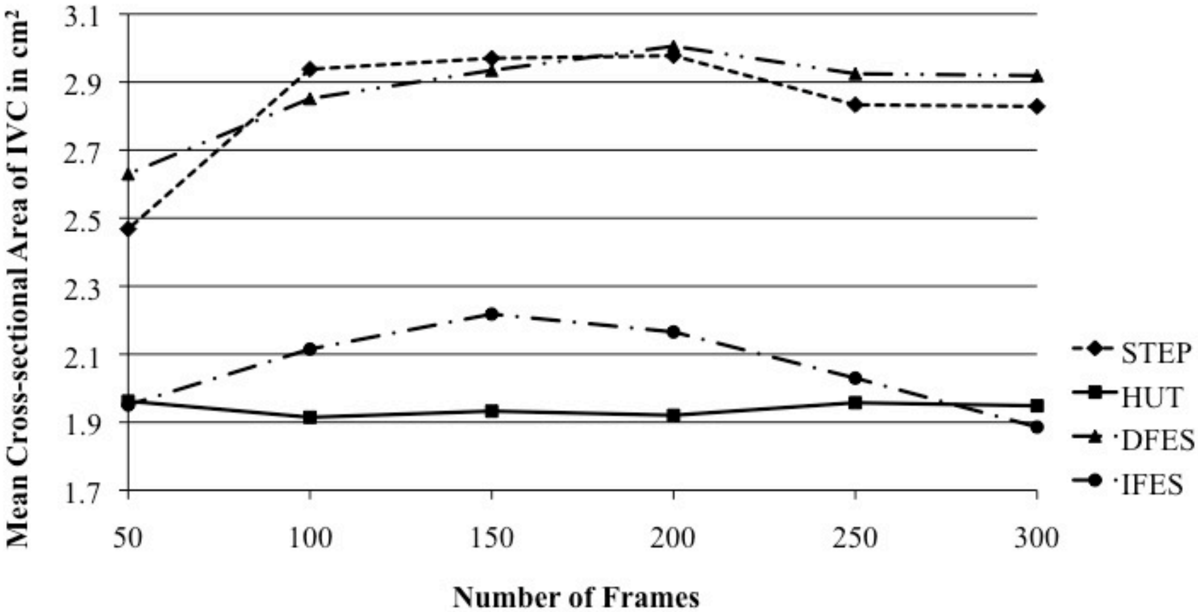

Figure 19: Measured mean cross-sectional area of the inferior vena cava (IVC) for Segment C. STEP represents imposed passive leg movements, HUT represents head-up tilt without intervention, DFES represents dynamic FES, and IFES represents isometric FES.

The normalized standard deviations in Figure 20 indicate that the length of an analyzed image sequence can affect the calculated mean area. To reduce this effect, 250 frames (corresponding to ten seconds of recording time) would be used for analysis. Figure 21 shows the mean cross-sectional areas calculated with 250 images. The variation between the three segments is small. However, the final results would be obtained by averaging the mean cross-sectional areas from all segments to account for the inter-segment variations.

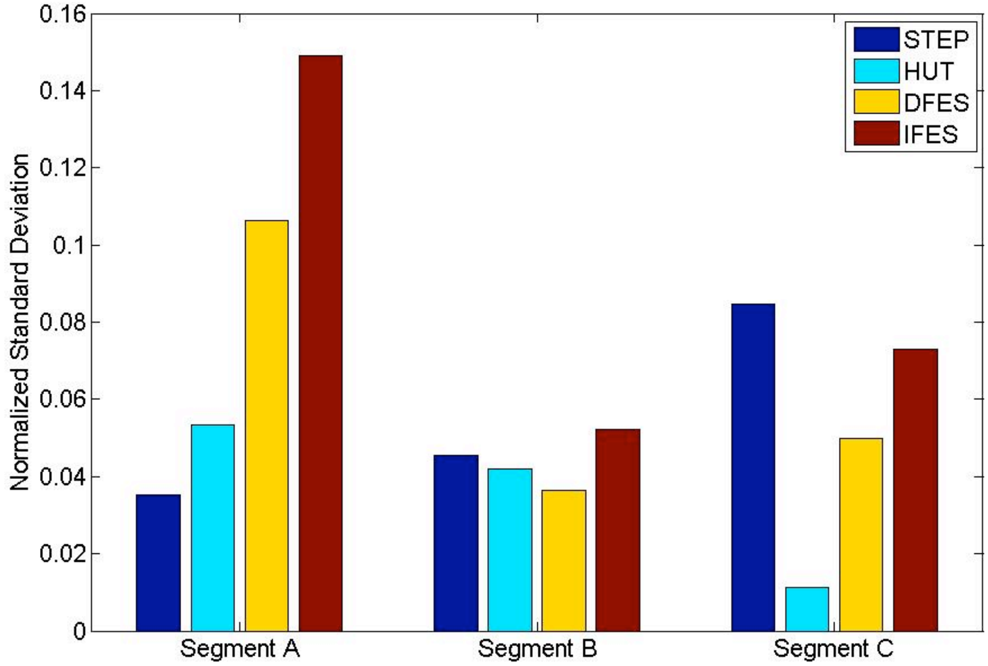

Figure 20: Normalized standard deviations of mean cross-sectional areas due to variation in segment length. Each bar represents the standard deviation of the cross-sectional area for a particular segment and test condition (in Figure 17 through Figure 19), normalized to its average value.

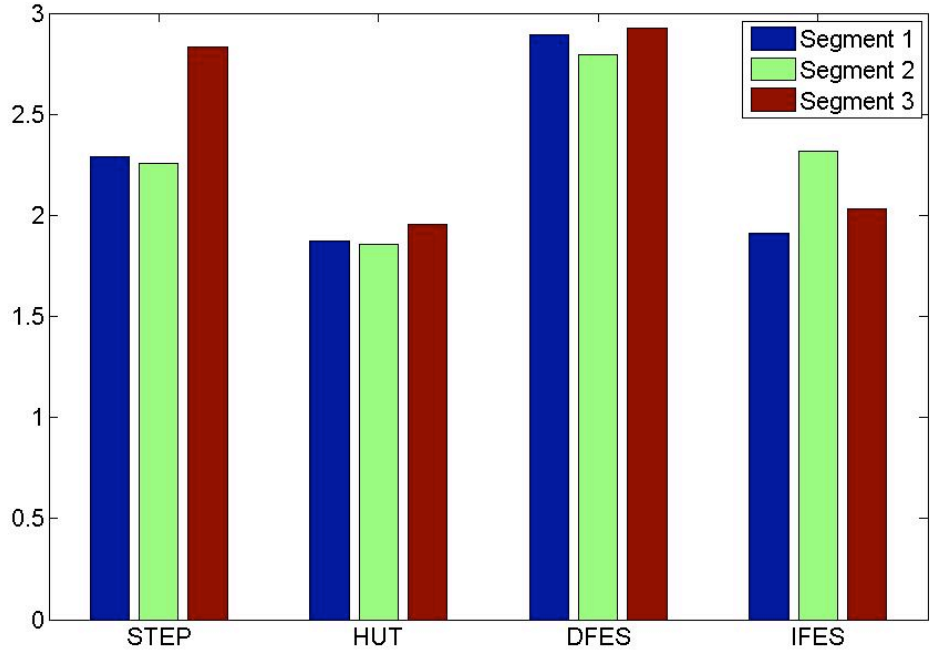

Figure 21: Mean cross-sectional areas calculated from 250 images, which corresponded to ten seconds of recording time at the conversion rate of 25 frames per second.

Next, the effect of decreasing the sampling frequency was examined. To decrease the effective sampling frequency from 25 Hz, the ultrasound images were analyzed at a constant interval. For example, effective sampling frequency of 5 Hz was obtained by analyzing only every fifth image in the sequence. Figure 22 through Figure 24 show the effect of reducing the sampling frequency for each segment. For this part of sensitivity analysis, all segments contained 250 images.

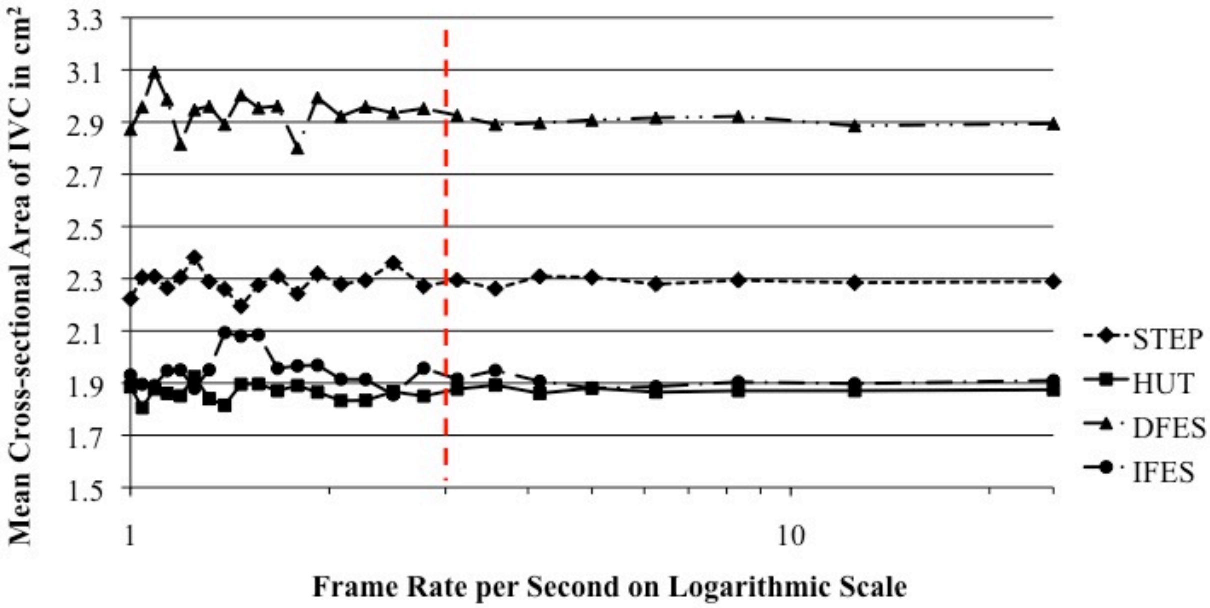

Figure 22: Measured mean cross-sectional area of the inferior vena cava (IVC) for Segment A. STEP represents imposed passive leg movements, HUT represents head-up tilt without intervention, DFES represents dynamic FES, and IFES represents isometric FES.

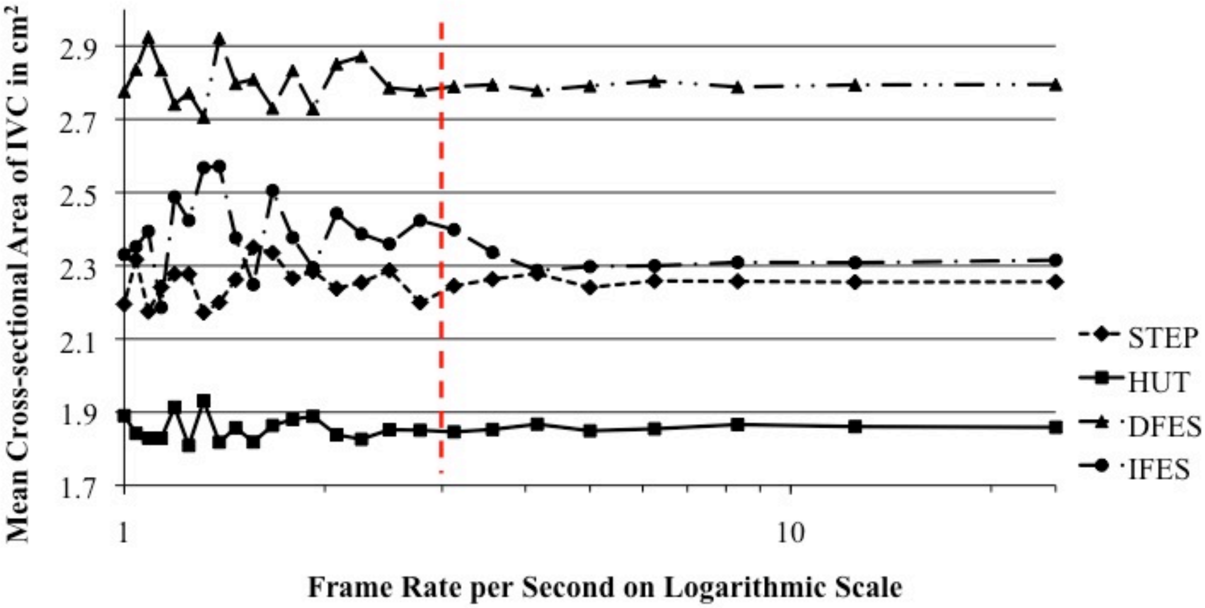

Figure 23: Measured mean cross-sectional area of the inferior vena cava (IVC) for Segment B. STEP represents imposed passive leg movements, HUT represents head-up tilt without intervention, DFES represents dynamic FES, and IFES represents isometric FES.

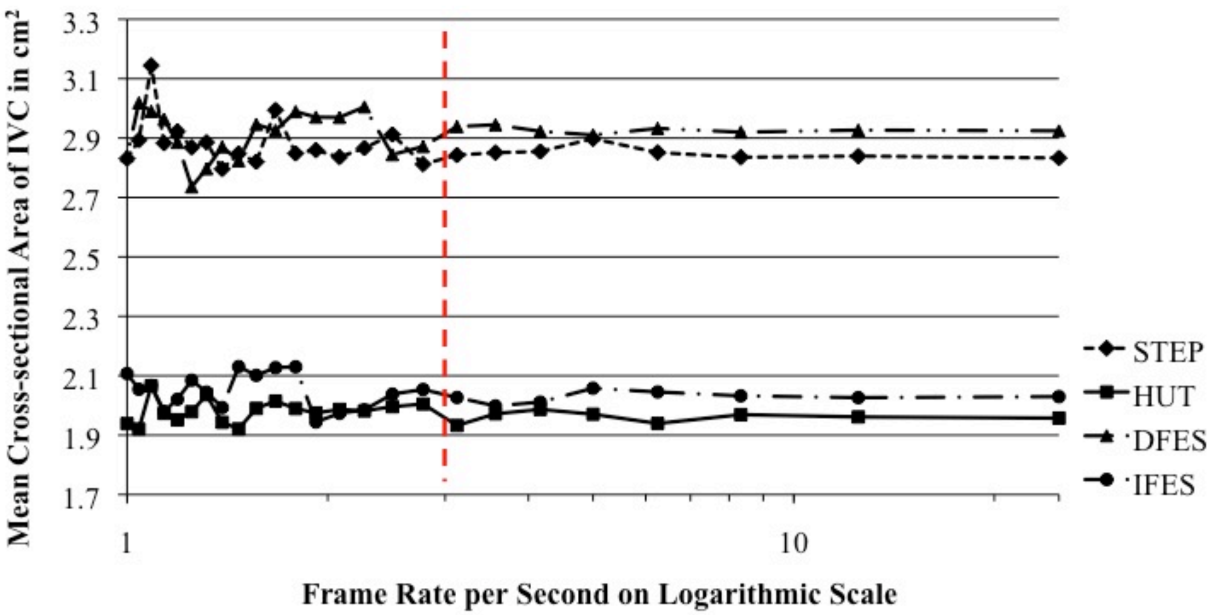

Figure 24: Measured mean cross-sectional area of the inferior vena cava (IVC) for Segment C. STEP represents imposed passive leg movements, HUT represents head-up tilt without intervention, DFES represents dynamic FES, and IFES represents isometric FES.

Figure 22 through Figure 24 illustrate that reducing the sampling frequency has very little effect on the calculated mean cross-sectional area of the inferior vena cava (see also Figure 25). However, small oscillations start to occur in all images sequences at frequencies below 2 Hz. Therefore, the sampling frequency of approximately 2 Hz was selected. With this frequency and segment length of 250 images, the investigator would only have to analyze 250 images per participant, instead of 6000 images.

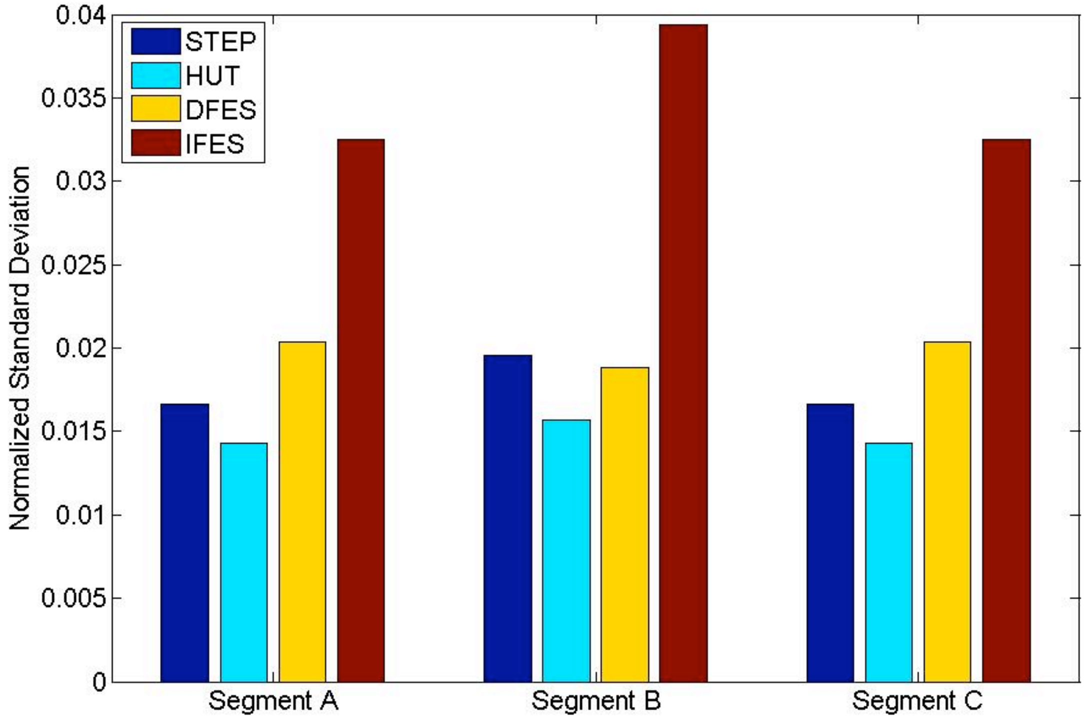

Figure 25: Normalized standard deviations of mean cross-sectional areas due to variation in sampling frequency. Each bar represents the standard deviation of the cross-sectional area for a particular segment and test condition (in Figure 22 through Figure 24), normalized to its average value.

3.5.2 Cardiovascular Data

All cardiovascular parameters were filtered using a low-pass, zero-phase digital filter, whose coefficients were provided by a first-order Butterworth filter with the cut-off frequency of 6 Hz. The cut-off frequency was selected by assuming that the maximum heart rate would not exceed 180 beats per minute. The cardiovascular monitoring system captured the arterial blood pressure waveforms at 200 Hz, which was well above the minimum recommended frequency of 30 Hz to capture undistorted arterial pressure waveforms [79]. Because we were interested in the average values over each minute, rather than the exact shape of the waveforms, the cut-off frequency of 6 Hz was deemed acceptable for this study.

3.5.3 Electromyograms

The EMG data was processed according to the procedure described by [93]. To process the EMG data, the full-wave rectified data was first filtered using a low-pass, zero-phase digital filter. The filter coefficients were provided by a first-order Butterworth filter with the cut-off frequency of 3 Hz. Then, a sample of 30 strides from the filtered data was averaged to remove the stride-to-stride variability. Finally, the standard deviations were calculated over the averaged stride, and the processed EMG data was plotted with the standard deviation.

3.5.4 Statistical Analysis

Once processed, statistical analysis was performed on the ultrasound and cardiovascular data. For all statistical analysis, the threshold to reject the null hypothesis was five percent ($p < 0.05$).

3.5.4.1 Cross-sectional Areas of the Inferior Vena Cava

Two-way factorial ANOVA was performed in a commercial numerical computing environment (MATLAB, The MathWorks, Inc., USA) to identify a statistically significant difference among the average cross-sectional areas of the IVC during each test condition. The first independent variable was the presence or absence of FES in the test condition, and the second independent variable was the presence or absence of passive leg movements in the test condition. If a statistically significant difference was confirmed, a multiple comparison test was performed after one-way factorial ANOVA to identify the test conditions that induced a significantly greater cross-sectional area of the IVC. For the multiple comparison tests, Turkey's honest significant difference criterion was used.

3.5.4.2 Cardiovascular Parameters

For cardiovascular parameters, three-way repeated measures ANOVA was performed in a commercial computing environment (MATLAB, The MathWorks, Inc., USA). The three independent variables were 1) the presence of absence of FES in the test condition; 2) the presence or absence of passive leg movements in the test condition; and 3) time. Two-way repeated measures ANOVA was also performed to determine if any test condition had a significant effect of the cardiovascular parameters. For the two-way ANOVA, the independent variables were 1) the test condition and 2) time.

Chapter 4: Results

4.1 Participants

Table 2 and Table 3 describe the participants for this study. Fifty percent of the participants were male. The average age of the participants was 41.3 years old (± 12.4), and their average body mass index was 30.5 kg/m^2 (± 4.46).

Table 2: Anthropometric data and the order of randomized test conditions for the participants. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Participant	Sex	Age	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	Order of Test Conditions
BBAA	F	47	157	91	37	HUT – IFES – DFES – STEP
BBAB	M	21	165	91	33	HUT – STEP – IFES – DFES
BBAC	F	38	170	77	27	STEP – IFES – HUT – DFES
BBAD	M	37	170	77	27	IFES – STEP – HUT – DFES
BBAF	M	57	183	110	33	STEP – IFES – DFES – HUT
BBAG	F	48	157	64	26	DFES – STEP – IFES – HUT

Table 3: Spinal cord pathology and relevant medical conditions of the participants. The relevance of medical conditions is based on their potential effect on the cardiovascular system.

Participant	Spinal Cord Pathology	Number of Years since Injury	Relevant Medical Conditions
BBAA	Non-traumatic, sensory incomplete, T6 paraplegia	6	Hypothyroidism Hypertension Type 2 diabetes Hyperlipidemia
BBAA	Motor and sensory complete, T1 paraplegia (AIS A)	10	Autonomic dysreflexia triggered by hot or cold temperatures or distended bowel or bladder
BBAC	Traumatic, incomplete, T2 paraplegia (AIS B)	11	Type 2 diabetes
BBAD	Traumatic, incomplete, C4 tetraplegia (AIS C)	13	N/A
BBAF	Traumatic, complete, C6 tetraplegia	3	N/A
BBAG	Traumatic, incomplete, C5 quadriplegia (AIS D)	1	Hypotension

Some participants had medical conditions that could potentially affect their cardiovascular system (see Table 3). However, these conditions were being managed through medication.

4.2 Prematurely Terminated Experiments

During the experiment, one participant (BBAB) reported symptoms associated with the onset of autonomic dysreflexia. The symptoms were described as numbness and spastic contractions that originated in the stomach and spread towards the head. After the symptoms were reported, the test condition was immediately terminated and the participant was returned to the supine position. Shortly after returning to the supine, the symptoms subsided. Throughout this event, the participant was fully conscious. The investigators tried to isolate the stimulus that caused the symptoms. However, the stimulus could not be specified. Due to the contamination of cardiovascular data by autonomic dysreflexia, this participant's data was excluded from the results.

4.3 Observed Episodes of OH

One participant (BBAG) reported dizziness during HUT. Table 4 shows the number of participants whose systolic or diastolic pressure indicated OH, based on the definition of OH [6,13].

Table 4: Number of participants that experienced OH, based systolic or diastolic blood pressure. To be classified as OH, a decrease in systolic pressure had to be equal to or greater than 20 mmHg, and a decrease in diastolic pressure had to be equal to or greater than 10 mmHg. Also, the decrease had to have occurred within three minutes of completing the head-up tilt. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Test Condition	Number of participants that experienced OH based on systolic pressure	Number of participants that experienced OH based on diastolic pressure
HUT	3 (BBAC, BBAD, BBAG)	1 (BBAC)
STEP	0	0
IFES	0	1 (BBAC)
DFES	1 (BBAC)	1 (BBAC)

4.4 Cardiovascular Responses

In all subsequent plots, the beat-to-beat cardiovascular parameters have been averaged over each minute: at each increment of the time scale (horizontal axis), the value represents an average over the preceding minute. For example, the value at the fourth minute is an average between the third and fourth minutes. All parameters have been normalized to the baseline value, which is an average from the last one minute of the supine rest, prior to the test condition. Also, all plots have been staggered and exclude the periods of tilting for visualization. The plots of cardiovascular parameters for individual participants can be found in Individual Cardiovascular Responses under Appendices.

4.4.1 Blood Pressures

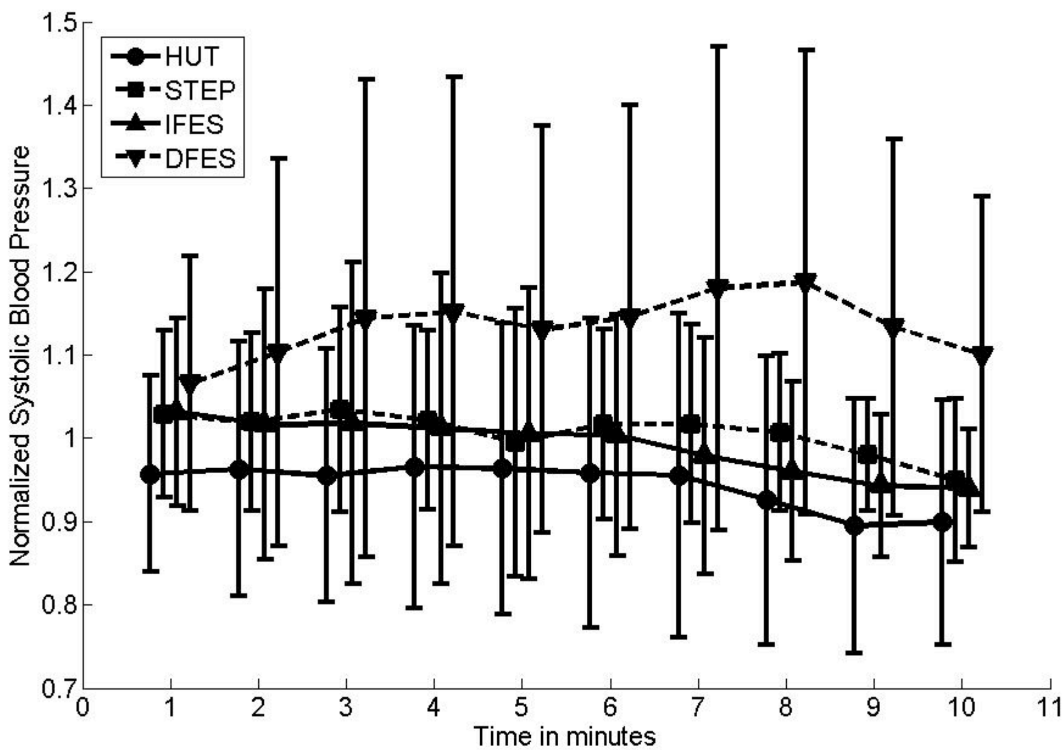

Figure 26: Normalized systolic blood pressure during test conditions. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

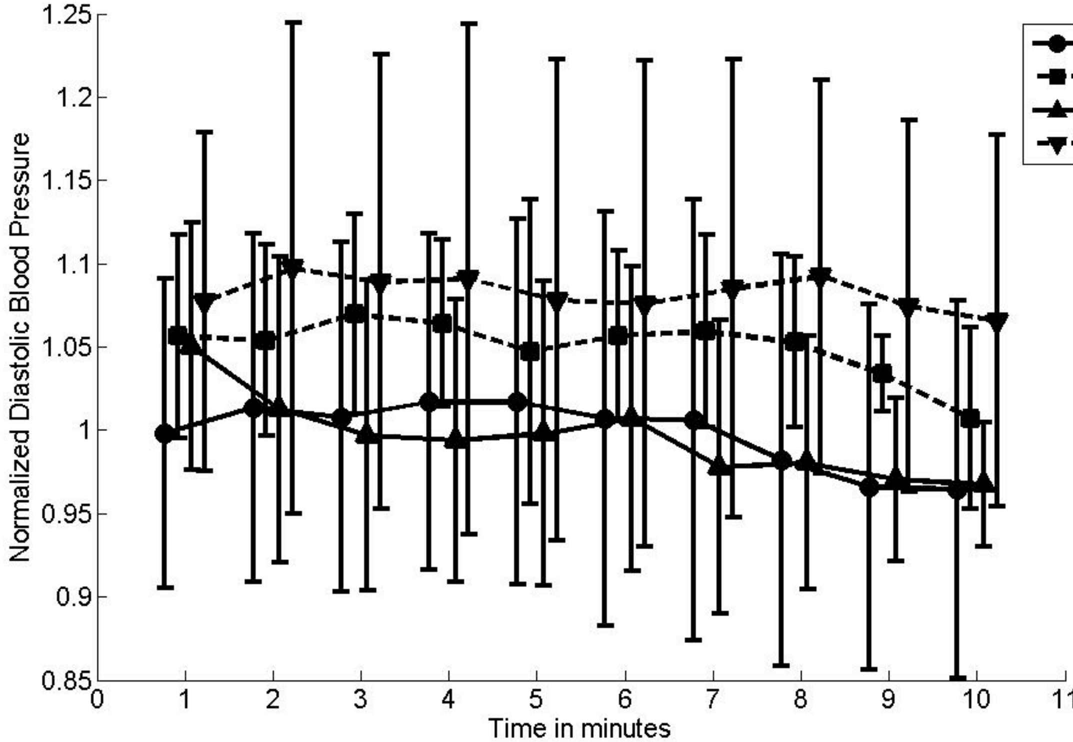

Figure 27: Normalized diastolic blood pressure during test conditions. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

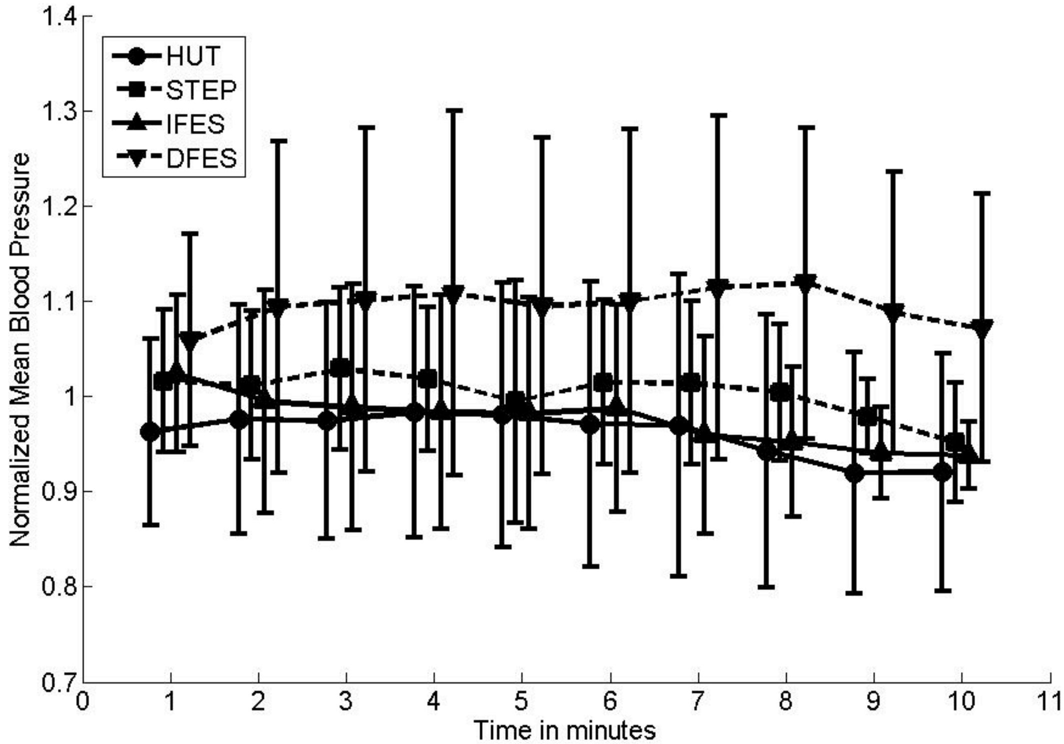

Figure 28: Normalized mean blood pressure during test conditions. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Figure 26 through Figure 28 show the systolic, diastolic, and mean blood pressures during each test condition. During HUT and STEP, the normalized diastolic blood pressure was greater than the normalized systolic pressure. Also, during HUT and STEP, both normalized pressures gradually decreased below their supine baseline values. Contrarily, the normalized systolic pressure was greater than the normalized diastolic pressure during DFES, and both normalized pressures were above the supine baseline values. During IFES, the normalized systolic and diastolic pressures gradually declined below their supine baseline values, but the normalized systolic pressure remained greater than the normalized diastolic pressure.

Three-way repeated measures ANOVA indicated that only passive leg movements had a significant effect on systolic ($F = 10.465$, $p = 0.0318$), diastolic ($F = 14.353$, $p = 0.0193$), and mean blood pressures ($F = 11.873,\ p = 0.0262$). The effect of FES was insignificant (see Table 5). The interaction between the effects of passive movements and FES was also insignificant for the blood pressures (see Table 5). Comparisons using two-way repeated measures ANOVA did not find significant differences in blood pressure on the basis of the presence or absence of passive leg movements, except for one pair. Instead, two-way repeated measures ANOVA found significant differences between DFES and HUT (see Table 6). The blood pressure during HUT and IFES did not differ significantly (see Table 6).

Table 5: F-ratios and *p* values for the effects of FES and passive leg movements on blood pressure, calculated by three-way repeated measures ANOVA.

Factor	Systolic Blood Pressure	Diastolic Blood Pressure	Mean Blood Pressure
FES	$F = 3.007$ $p = 0.1579$	$F = 0.265$ $p = 0.6336$	$F = 2.463$ $p = 0.1916$
Passive Stepping	$F = 10.465$ $p = 0.0318$	$F = 14.353$ $p = 0.0193$	$F = 11.873$ $p = 0.0262$
Interaction: FES×Passive Stepping	$F = 0.717$ $p = 0.4448$	$F = 0.224$ $p = 0.6604$	$F = 1.192$ $p = 0.3363$

Table 6: F-ratios and *p* values for selective comparisons of blood pressures using two-way repeated measures ANOVA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Comparison	Systolic Blood Pressure	Diastolic Blood Pressure	Mean Blood Pressure
HUT vs. STEP	$F = 1.2542$ $p = 0.3255$	$F = 1.1832$ $p = 0.3379$	$F = 0.9070$ $p = 0.3948$
IFES vs. DFES	$F = 6.1156$ $p = 0.0687$	$F = 7.0438$ $p = 0.0567$	$F = 9.3275$ $p = 0.0379$
HUT vs. DFES	$F = 8.3168$ $p = 0.0448$	$F = 8.0397$ $p = 0.0471$	$F = 9.9025$ $p = 0.0346$
HUT vs. IFES	$F = 4.4080$ $p = 0.1037$	$F = 0.0080$ $p = 0.9330$	$F = 0.2881$ $p = 0.6199$

4.4.2 Heart Rate

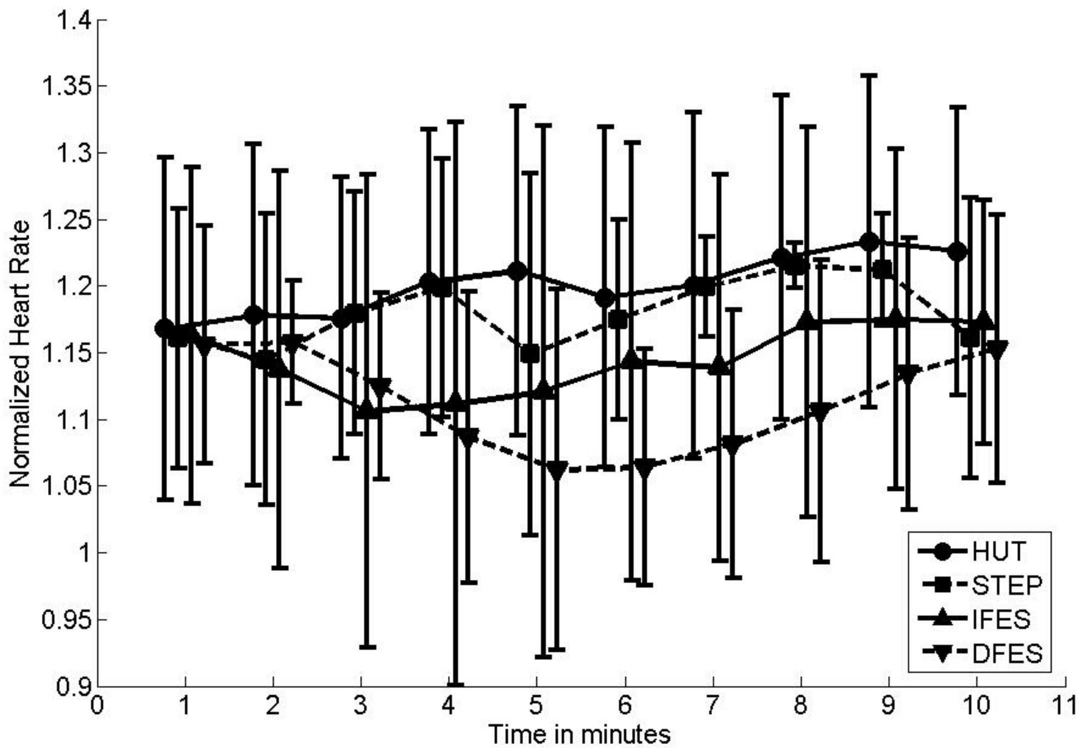

Figure 29: Normalized heart rate during test conditions. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

In individuals with SCI, postural tachycardia is expected. All test conditions resulted in higher heart rate than the supine baseline value. The two test conditions with FES somewhat reduced the increase in heart rate; DFES was more effective than IFES. According to three-way repeated measures ANOVA, neither FES ($F = 3.209$, $p = 0.1477$) nor passive leg movements ($F = 1.056$, $p = 0.3622$) significantly affected heart rate. The interaction between the effects of passive leg movements and FES was also insignificant ($F = 0.06$, $p = 0.8185$). According to two-way repeated measures ANOVA, there was no significant difference between HUT and any other test condition (see Table 7).

Table 7: F-ratios and *p* values for comparisons of heart rate using two-way repeated measures ANOVA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

	HUT vs. STEP	HUT vs. IFES	HUT vs. DFES
F-ratio	0.4914	1.2845	4.5031
***p* value**	0.5219	0.3204	0.1011

4.4.3 Stroke Volume

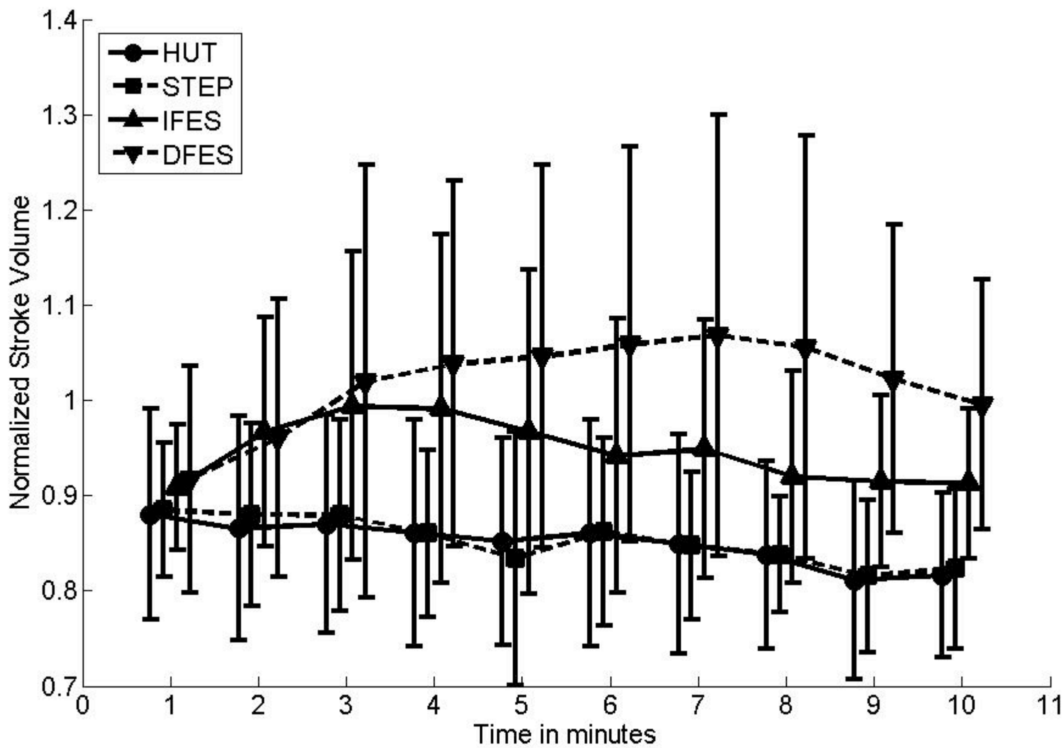

Figure 30: Normalized stroke volume during test conditions. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

The plotted stroke volumes illustrate that, without intervention or passive leg movements alone, stroke volume gradually decreased and remained below the supine value. On average, IFES was more effective in maintaining stroke volume. However, it was still below the baseline. Contrarily, DFES maintained stroke volume above the baseline for the majority of its duration.

Three-way repeated measures ANOVA indicated a significant effect of FES on stroke volume ($F = 8.427,\ p = 0.044$), whereas the effect of passive leg movements was insignificant ($F = 1.383,\ p = 0.3048$). The effects of FES and passive leg movements did not interact significantly ($F = 2.39,\ p = 0.197$). The results of comparisons using two-way repeated measures ANOVA are shown in Table 8.

Table 8: F-ratios and *p* values for comparisons of stroke volume using two-way repeated measures ANOVA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

	STEP vs. DFES	HUT vs. IFES	HUT vs. STEP	HUT vs. DFES
F-ratio	9.0958	4.4731	0.0045	7.3126
***p* value**	0.0393	0.1019	0.9495	0.0539

4.4.4 Systemic Vascular Resistance

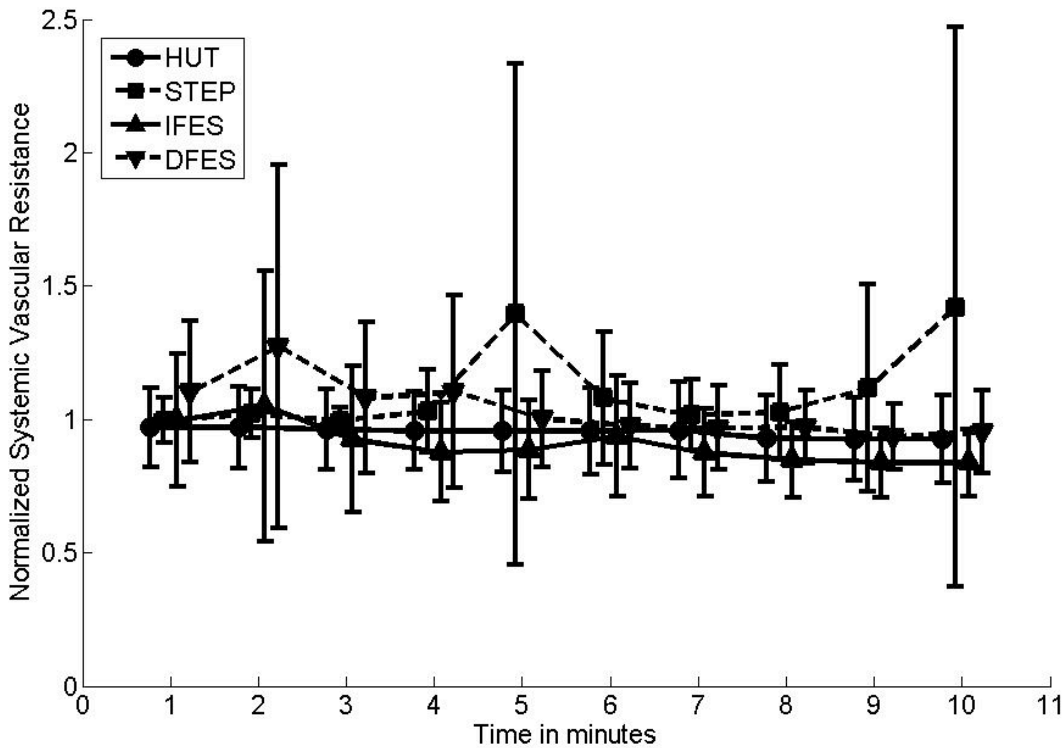

Figure 31: Normalized systemic vascular resistance during test conditions. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

In Figure 31, the peaks at the fifth and tenth minutes of STEP were the contributions from one participant (BBAA). Similarly, the peak at the second minute of DFES was the contribution from one participant (BBAF). This explains the relatively large standard deviations at these points. Other than these peaks, the systemic vascular resistance remained relatively constant during all test conditions. Although three-way repeated measures ANOVA indicated a significant effect of passive leg movements on systemic vascular resistance ($F = 10.825$, $p = 0.0302$), this is most likely due to the contribution of aforementioned peaks. The effect of FES was insignificant ($F = 0.388$, $p = 0.5669$), and the interaction between the effects of FES and passive leg movements was insignificant ($F = 0.042$, $p = 0.8477$). Two-way repeated measures ANOVA revealed no significant difference on the basis of passive leg movements (see Table 9).

Table 9: F-ratios and *p* values for comparisons of systemic vascular resistance using two-way repeated measures ANOVA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

	HUT vs. STEP	IFES vs. DFES	HUT vs. DFES
F-ratio	2.2812	6.2055	1.8731
***p* value**	0.2055	0.0674	0.2429

4.5 Cross-sectional Area of Inferior Vena Cava

The ultrasound imaging of the IVC has been completed for Participants BBAD and BBAF because a clear image of the IVC could not be obtained for the remaining participants. During ultrasonography, obesity is often associated with poor image quality [94], possibly due to the absence of an adequate acoustic window or greater scattering and absorption of ultrasound by the tissue [95]. This may explain, at least partially, why it was difficult to obtain clear images of the IVC for three of the five participants: based on the body mass index, all participants were overweight [5]. However, obesity does not independently determine the image quality in ultrasonography [94]. At least for this study, clear image could not be obtained for all female participants. Also, image quality is more susceptible to tissue interaction for an imaging frequency at or higher than 5 MHz [96], which was the frequency used in this study.

Figure 32 and Figure 33 show the calculated cross-sectional areas of the IVC during each test condition for two participants. Each bar represents the average value of a one-minute recording. These average values have been normalized to the value during a head-up tilt wihout intervention.

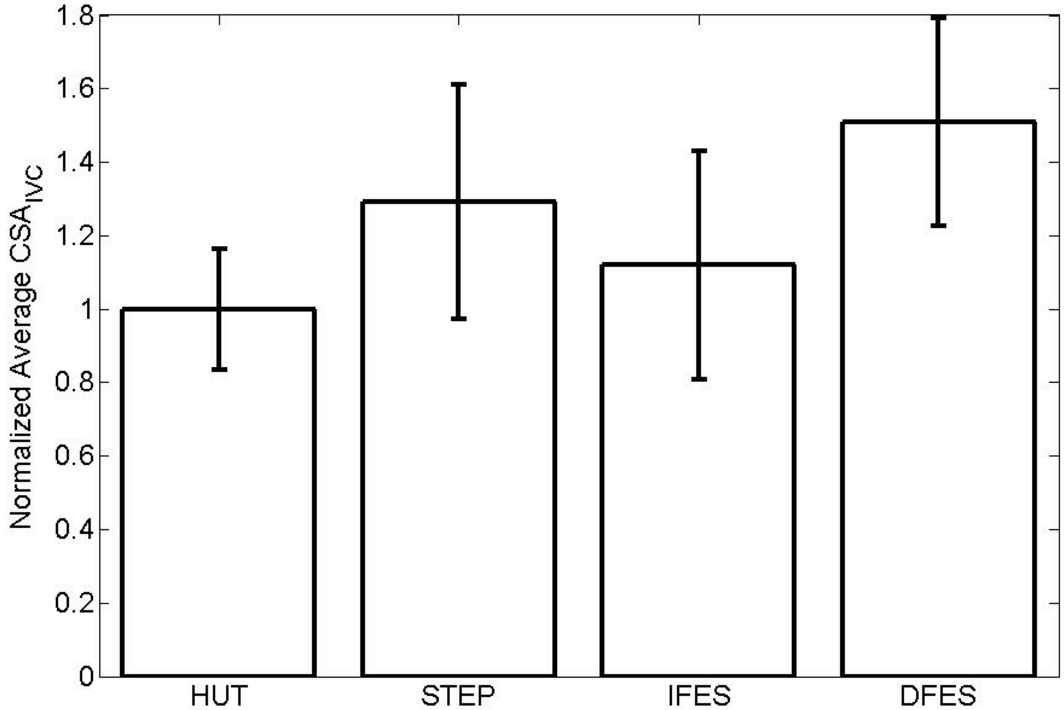

Figure 32: Average cross-sectional areas of the IVC (CSA_{IVC}) for participant BBAD. All areas have been normalized to HUT. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

For participant BBAD, two-way factorial ANOVA revealed that FES ($F = 23.41,\ p < 0.0001$) and passive leg movements ($F = 95.93,\ p < 0.0001$) both had a significant effect on the cross-sectional area of the IVC. There was no significant interaction between the two effects ($F = 2.01,\ p = 0.157$). Further analysis using a multiple comparison test revealed that the mean cross-sectional area of the IVC was significantly different during each test condition ($p < 0.0001$). DFES induced the largest mean cross-sectional area, followed by STEP, IFES, and HUT, in the descending order.

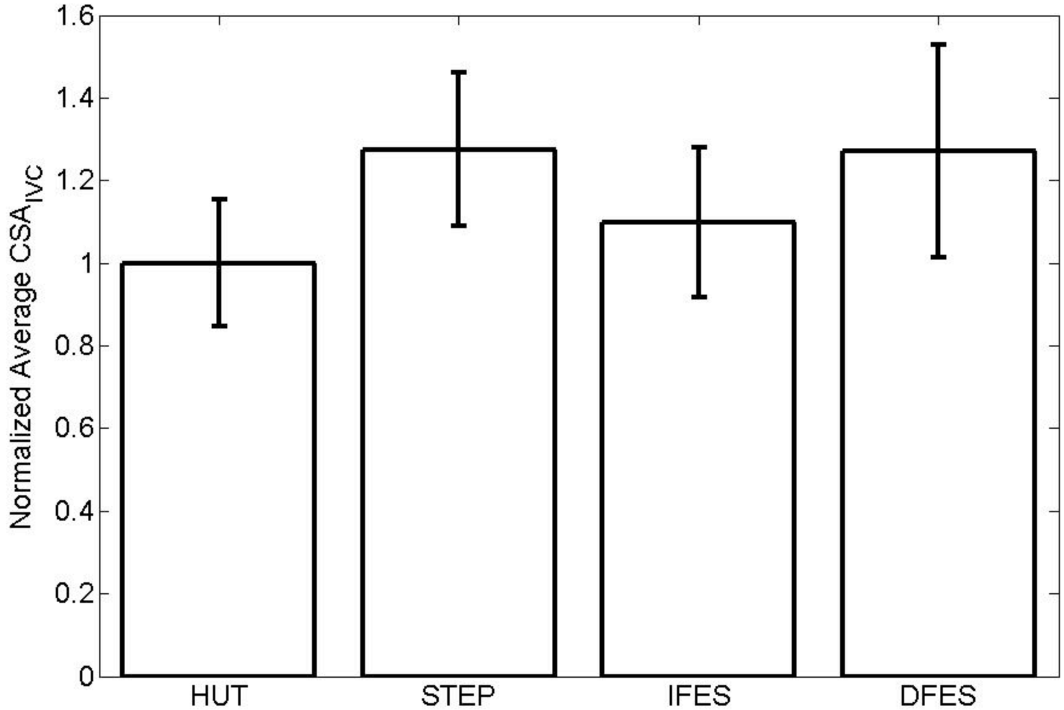

Figure 33: Average cross-sectional areas of the IVC (CSA_{IVC}) for participant BBAF. All areas have been normalized to HUT. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

For participant BBAF, the presence or absence of FES did not have a significant effect on the cross-sectional area of the IVC ($F = 3.54,\ p = 0.0611$), whereas the presence or absence of passive leg movements did ($F = 80.73,\ p = 0.00$). The interaction between the effects of FES and passive leg movements was significant ($F = 4.06,\ p = 0.045$). The subsequent multiple comparison test confirmed that both STEP and DFES induced significantly greater cross-sectional areas of the IVC, compared to IFES and HUT ($p < 0.0001$).

4.6 Electromyograms

The EMG data have been processed for Participants BBAA and BBAG. The data for the remaining participants were affected by noise that could not be removed through filtering. This noise was generated when the participant's skin came in contact with the tilt table and was attributed to the vulnerability of the EMG measurement system. Figure 34 and Figure 35 show the average EMG activities of eight muscles over one stride, recorded during STEP.

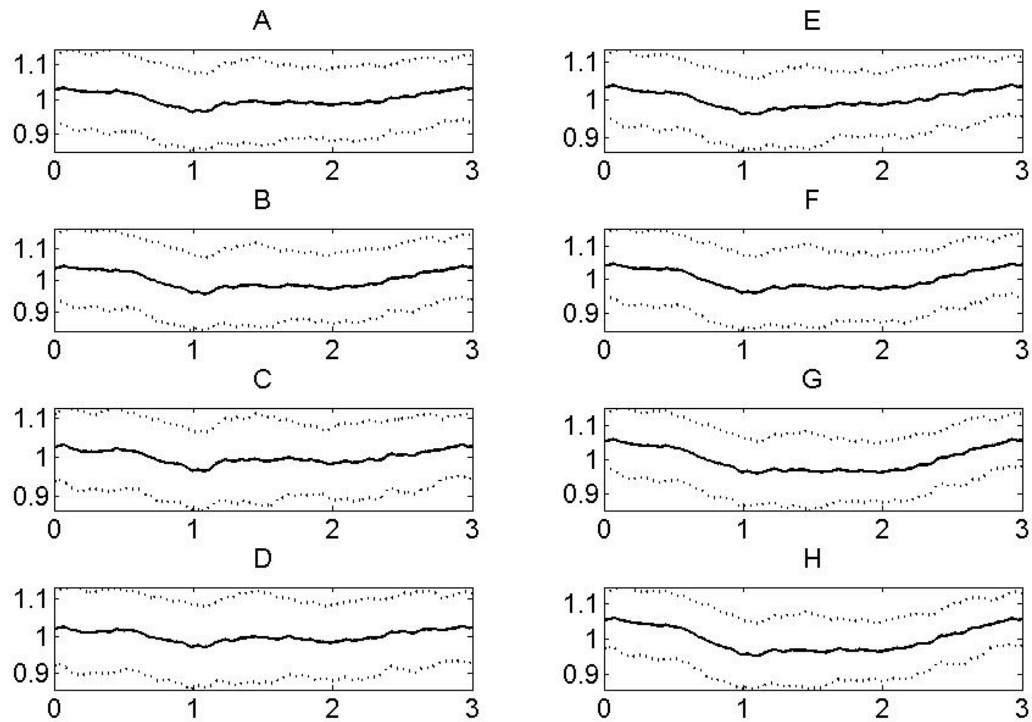

Figure 34: Electromyograms for Participant BBAA during one stride. Subplot A represents the left rectus femoris, B represents the left biceps femoris, C represents the left tibialis anterior, and D represents the left medial gastrocnemius. Subplots E, F, G, and H represent the right leg muscles in the same order as subplots A, B, C, and D. For all subplots, the vertical axis represents the normalized EMG activity and the horizontal axis represents time in seconds. The solid line represents the average electromyogram of 30 strides, and the dotted lines represent the standard deviations. The EMG activities have been normalized to the average value during one stride.

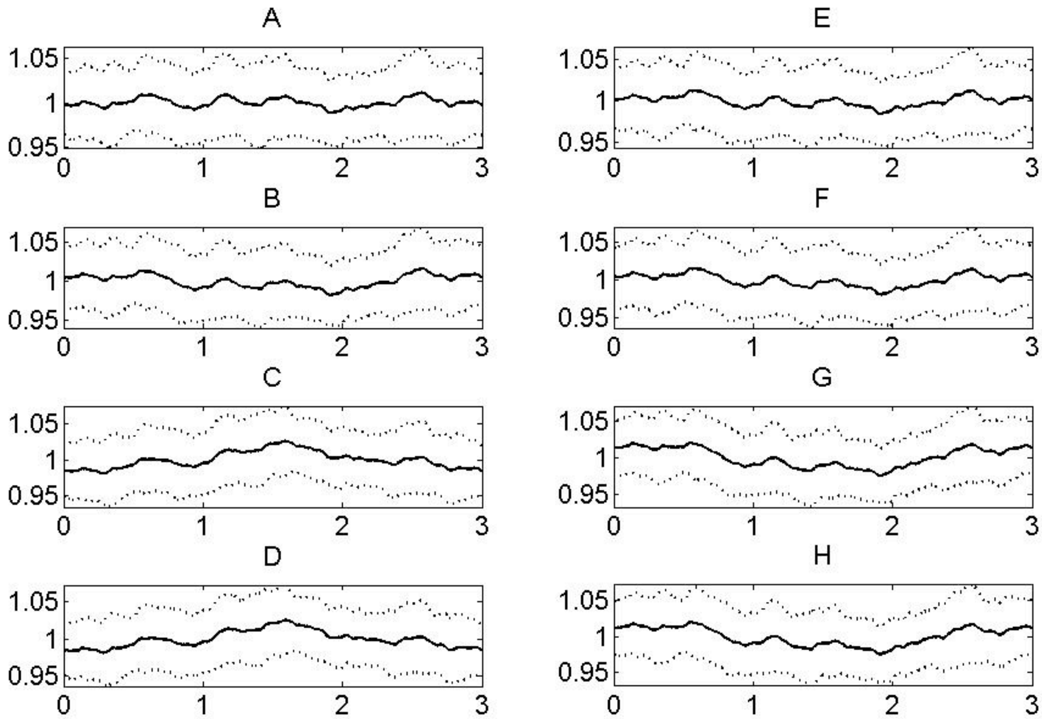

Figure 35: Electromyograms for Participant BBAG during one stride. Subplot A represents the left rectus femoris, B represents the left biceps femoris, C represents the left tibialis anterior, and D represents the left medial gastrocnemius. Subplots E, F, G, and H represent the right leg muscles in the same order as subplots A, B, C, and D. For all subplots, the vertical axis represents the normalized EMG activity and the horizontal axis represents time in seconds. The solid line represents the average electromyogram of 30 strides, and the dotted lines presents the standard deviations. The EMG activities have been normalized to the average value during one stride.

Chapter 5: Discussions

5.1 Cardiovascular Responses

Based on the decrease in systolic pressure, three participants experienced OH during HUT and one participant experienced OH during DFES. Based on the decrease in diastolic pressure, HUT, IFES, and DFES each induced OH in one participant. However, only one participant reported dizziness during HUT. The mismatch between the self-reported symptoms and recorded decrease in blood pressure is most likely due to the adaptation to hypotension in individuals with SCI [6]. Indeed, the participant that reported dizziness was only one-year post SCI, whereas other participants were at least three-years post SCI.

Because systemic vascular resistance remained relatively unchanged and heart rate generally increased during each test condition, the observed progressions of blood pressure implied a specific change in stroke volume. During HUT and STEP, stroke volume decreased. During IFES, stroke volume decreased but not as much as during HUT or STEP. During DFES, stroke volume increased. These implications were verified by the measured stroke volume. Because DFES was designed to maintain the arterial blood pressure by inducing venous return, the observed increase in stroke volume supports the efficacy of DFES. Furthermore, on average, DFES maintained mean arterial pressure above the supine baseline value, while other interventions failed to do so.

Between the four test conditions, heart rate and systemic vascular resistance did not differ significantly. Therefore, the observed differences in blood pressure among the test conditions must have been due to the differences in stroke volume. Because stroke volume was primarily induced by the applied interventions (STEP, IFES, and DFES), the changes in arterial blood pressure effectively indicated the performance of each intervention: among the four test conditions, DFES best maintained the arterial blood pressure during a head-up tilt. Maintaining arterial pressure would have ensured sufficient cerebral perfusion, and this would reduce the chance of experiencing OH for individuals with SCI that are more susceptible to orthostatic stress. Importantly, FES or passive leg movements alone did not perform as well as DFES. Therefore, during a head-up tilt, both passive movements and active muscle contractions in the lower limbs seem necessary to improve the cardiovascular response of individuals with SCI.

5.2 Stroke Volume vs. Cross-sectional Areas of the IVC

On average, DFES induced the largest mean cross-sectional area of the IVC, which was significantly larger than the cross-sectional area during HUT. Multiple comparison tests also indicated a synergistic effect of FES and passive leg movements on the cross-sectional area of the IVC. Assuming that the cross-sectional area changed in proportion to the central venous pressure, the area should reflect the venous return during each test condition. In other words, the relative magnitudes of the cross-sectional areas (between test conditions) should correspond to the relative magnitudes of the measured stroke volumes, based on the Frank-Starling mechanism. However, the measured stroke volumes somewhat disagreed with the calculated cross-sectional areas of the IVC, which suggested that STEP (not IFES) induced the second greatest venous return. There are several possible causes for this discrepancy. First, the investigators assumed that an increase in the cross-sectional area of the IVC would indicate increased central venous pressure due to the influx of blood towards the right atrium. However, this correlation between the cross-sectional area of the IVC and central venous pressure is only accurate at the entrance to the right atrium [91,92]. Also, the influx of venous blood could have been impeded by the right atrial pressure or pressure associated with respiration. Without observing all sources of resistance at the junction of the IVC and the right atrium, it is difficult to explain the discrepancy definitively. Finally, the cross-sectional areas of the IVC were calculated for two out of five participants; further analysis with more participants may change the relative magnitudes of the cross-sectional areas.

5.3 Electromyograms

Compared to the EMG activities observed in other studies [68-71], the EMG activities in Figure 34 and Figure 35 were minimal, and no distinct patterns could be identified. The relatively small range of hip motion and slow rate of passive movements may have been insufficient to activate the central pattern generator [68-71]. The extent of weight bearing, which could not be quantified in this study, may have also been insufficient. Lastly, the design of the tilt table did not allow any hip extension, and this too could have contributed to the absence of rhythmic EMG activities. A further investigation is necessary to determine whether the extent of weight bearing and the kinematics of imposed passive leg movements in this study satisfy the requirements for observing rhythmic EMG activities.

5.4 Future tasks

This study needs data from more individuals with SCI. If the observed trends in the cardiovascular response can be confirmed with a larger sample of participants, the efficacy of dynamic FES will be better substantiated. Also, the study should further explore whether the passive movements on the novel tilt table can activate the central pattern generator. If the results remain favorable after further investigation, then the long-term effects of dynamic FES should be investigated in a clinical study, with a larger population of individuals with SCI. The study should target newly acquired injuries and monitor the effects of dynamic FES for approximately two months. Because most of the muscle atrophy and bone loss occur within the first year post injury, early intervention is critical for preventing secondary complications associated with immobilization [21,23,25,26]. The future study should monitor muscle mass of the lower extremities, fatigue resistance of the lower extremity muscles, bone loss, orthostatic tolerance, and perceived well-being of the participants. Each participant should receive the therapy for at least one hour per day, five times a week.

5.5 Limitations

5.5.1 Measuring Venous Return

Dynamic FES was designed to maintain blood pressure by inducing adequate venous return under orthostatic stress. Therefore, venous return was an important measurement to prove the proposed mechanism. However, this study only measured the cross-sectional area of the IVC as a surrogate for venous return. The lack of velocity measurement should not be overlooked because there is no clear and well-supported relationship between the instantaneous cross-sectional area of the IVC and its volumetric flow. The investigators were unable to measure the continuous volumetric flow through the IVC, and the attempt to measure the instantaneous velocity of venous return using Doppler ultrasound yield unreliable results.

5.5.2 Quantifying Weight Bearing during Head-up Tilt

In this study, weight bearing was only confirmed visually. In future studies, the extent of weight bearing should be quantified because it plays an important role in activating the central pattern generator of the human bipedal locomotion. If passive leg movements can activate the central pattern generator, the induced EMG activities will contribute to facilitating venous return and to increasing cardiac output.

Chapter 6: Conclusions

Although blood pressure was significantly affected by the presence or absence of passive leg movements in the test condition, dynamic FES was the only intervention that successfully maintained the arterial pressure during a 70-degree head-up tilt. The efficacy of dynamic FES can be attributed to its ability to induce venous return under increased orthostatic stress, thus maintaining sufficient stroke volume. The results also indicated that the effects of FES and passive leg movements on the cardiovascular response are generally additive, and FES or passive leg movements alone is insufficient to prevent undesirable responses. This is most likely due to the optimized venous-pump effect of dynamic FES. During isometric FES, FES-induced contractions are resisted by the fixation of posture. Contrarily, during dynamic FES, FES is applied while muscles are shortening. This stimulation pattern implies that dynamic FES causes greater compression of lower limb veins. By combining FES and passive leg movements into one intervention, it can help prevent possible episodes of OH in individuals with SCI. Although further investigation is needed, dynamic FES may enable more individuals with SCI to participate in beneficial neurorehabilitation, especially in the acute phase of the injury.

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Appendices

Individual Cardiovascular Responses

Systolic Blood Pressure

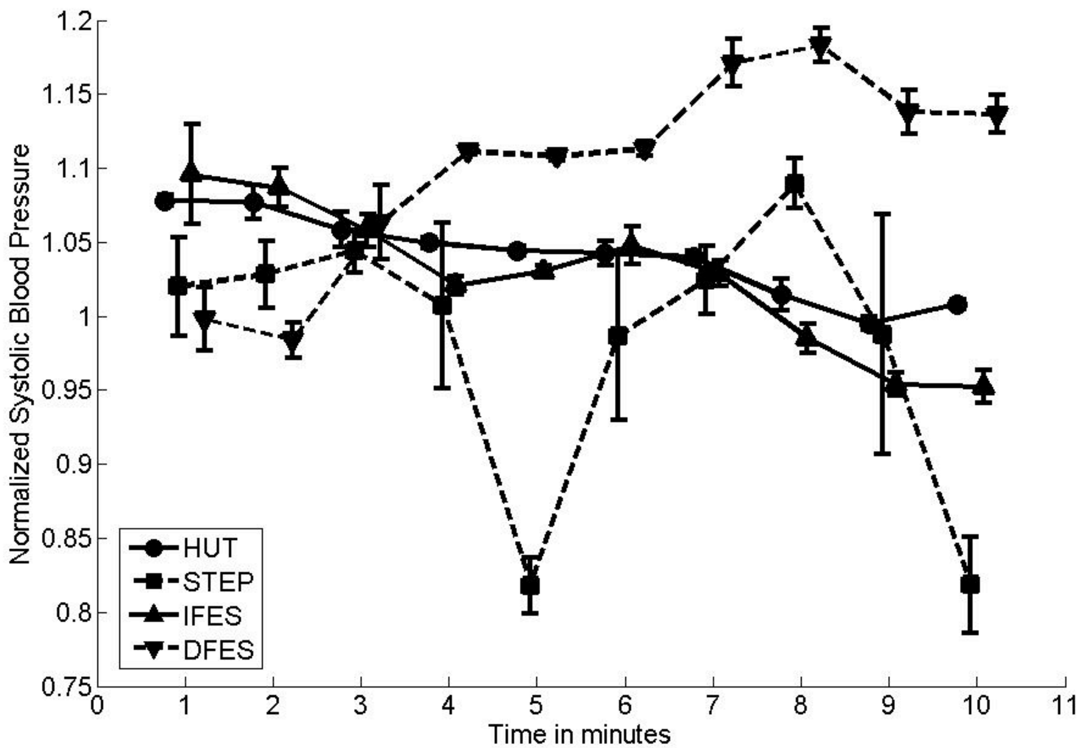

Figure 36: Normalized systolic blood pressure for Participant BBAA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

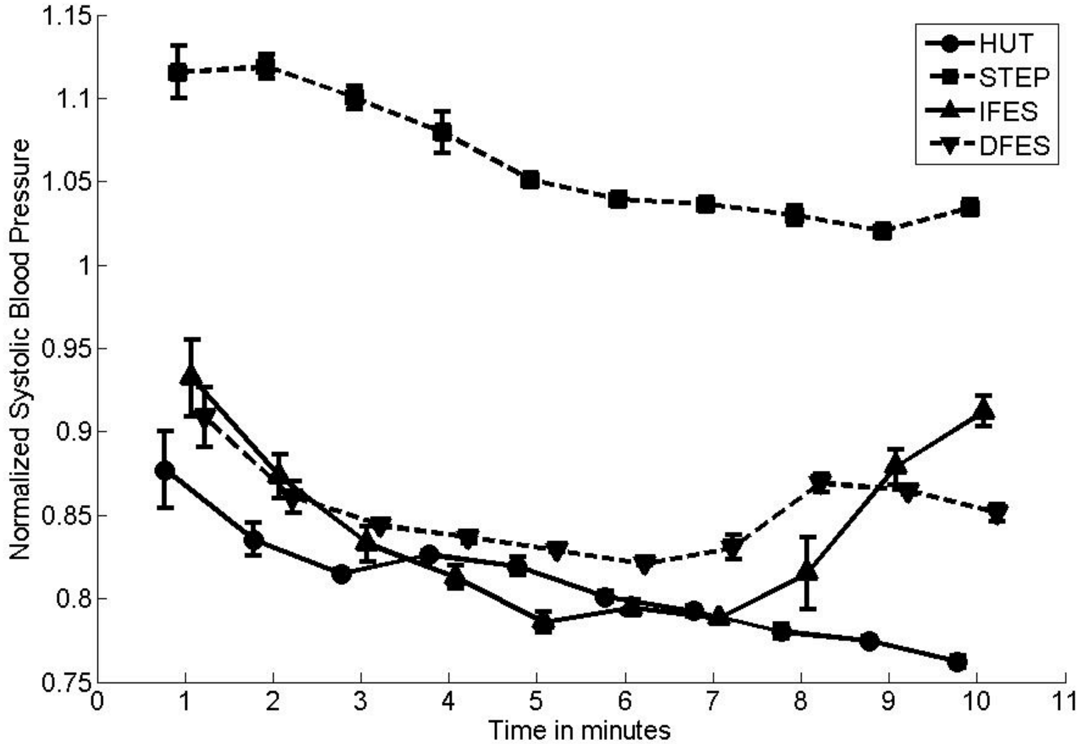

Figure 37: Normalized systolic blood pressure for Participant BBAC. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

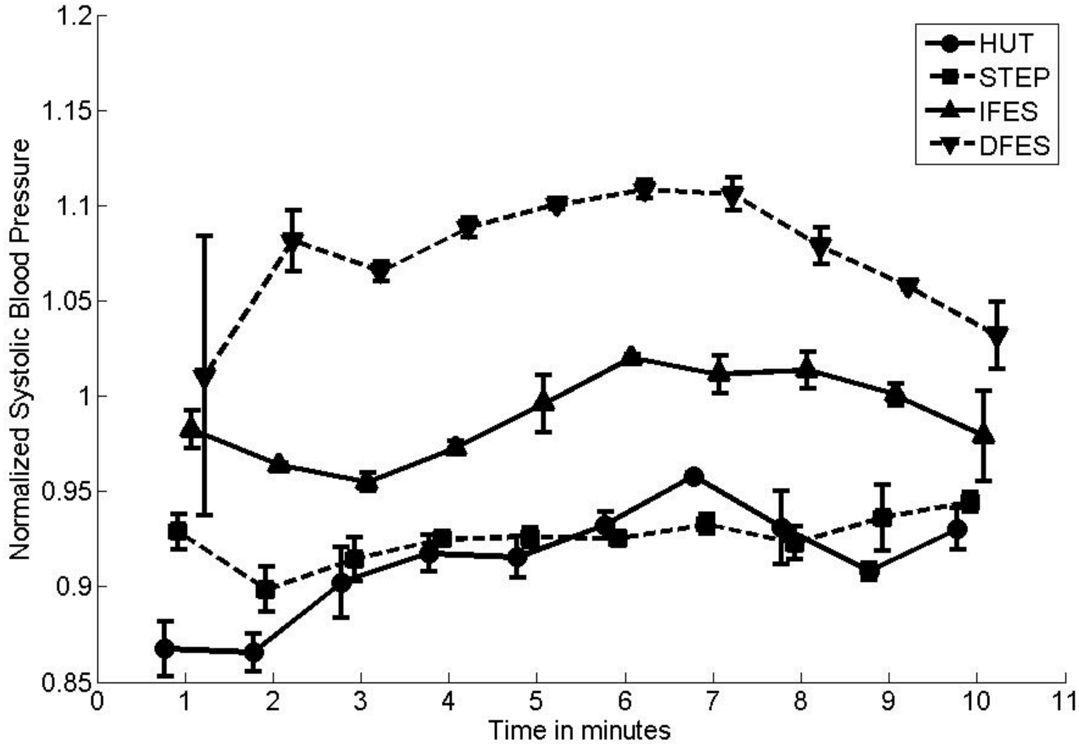

Figure 38: Normalized systolic blood pressure for Participant BBAD. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

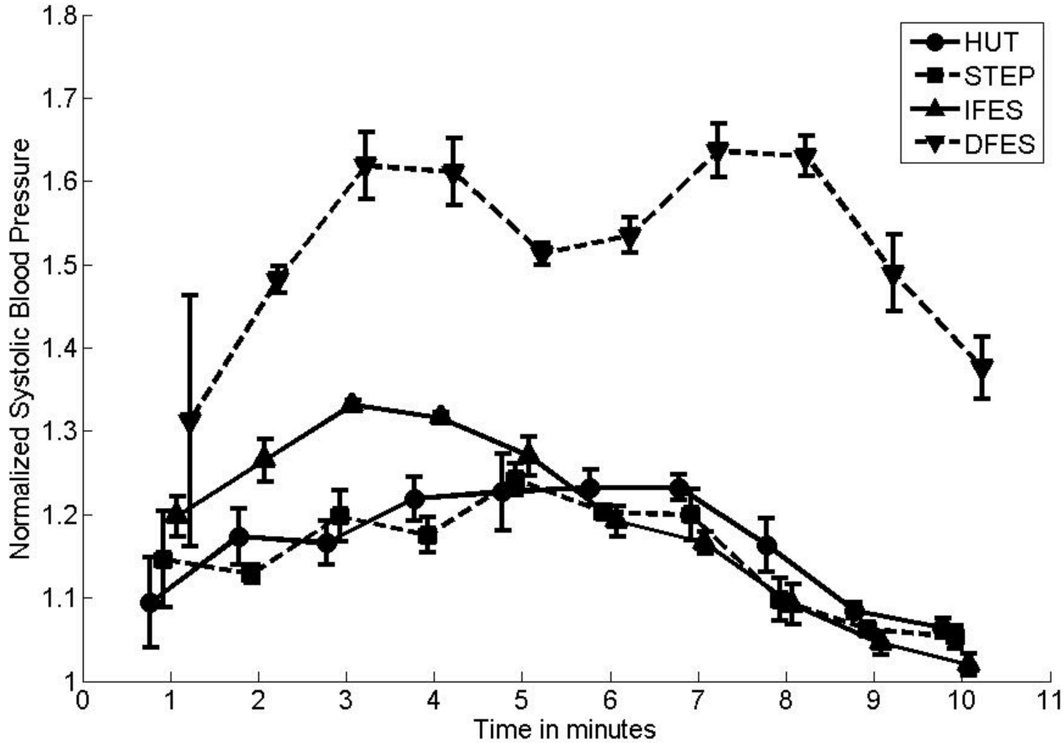

Figure 39: Normalized systolic blood pressure for Participant BBAF. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

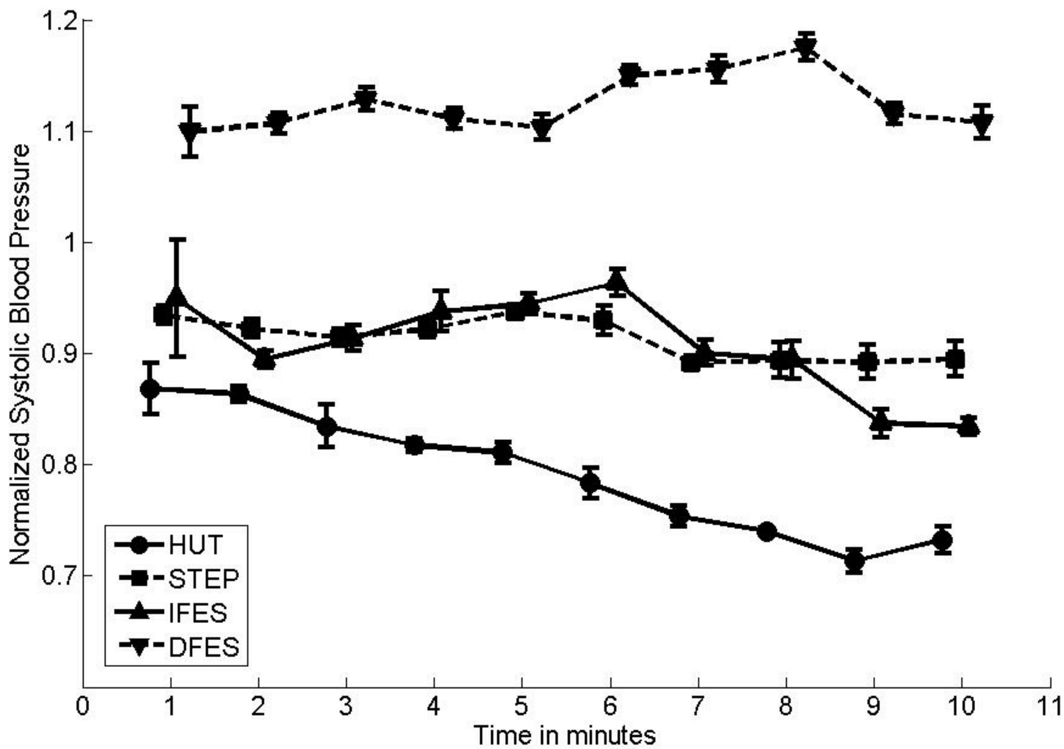

Figure 40: Normalized systolic blood pressure for Participant BBAG. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Diastolic Blood Pressure

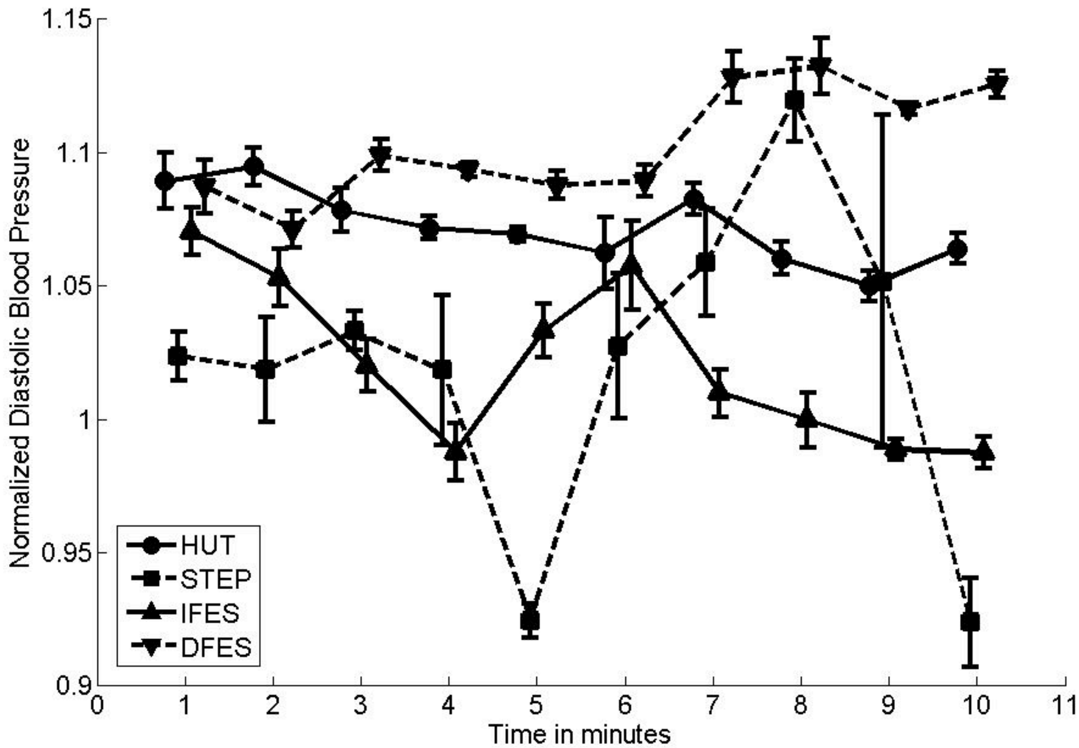

Figure 41: Normalized diastolic blood pressure for Participant BBAA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

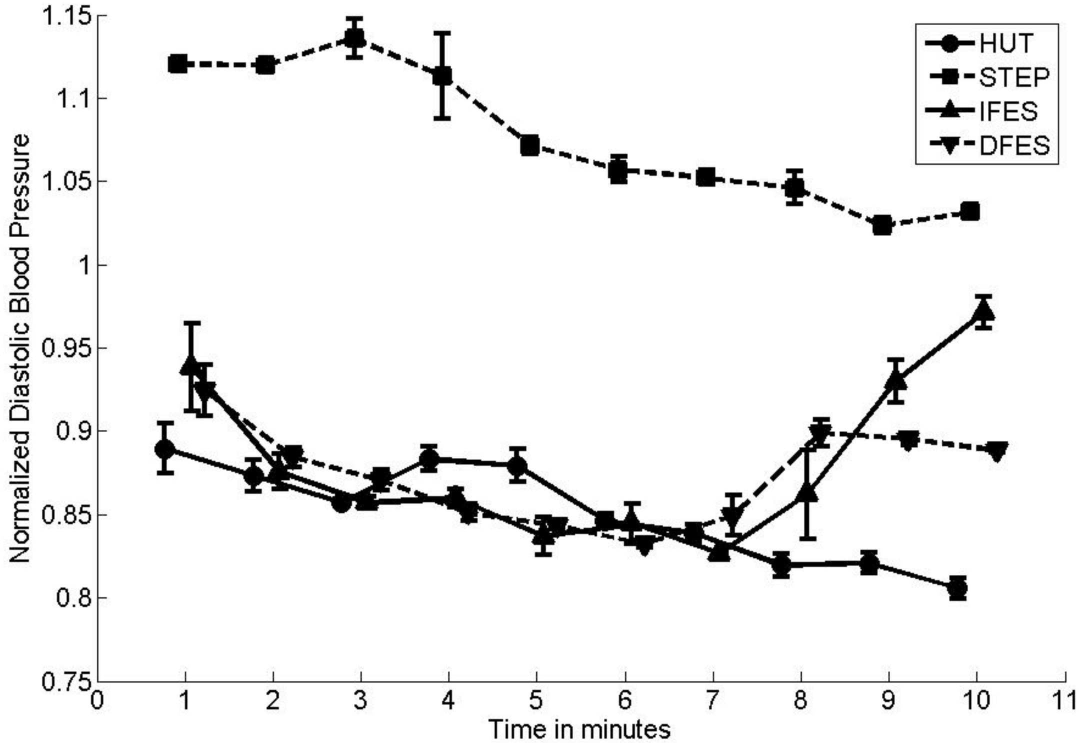

Figure 42: Normalized diastolic blood pressure for Participant BBAC. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

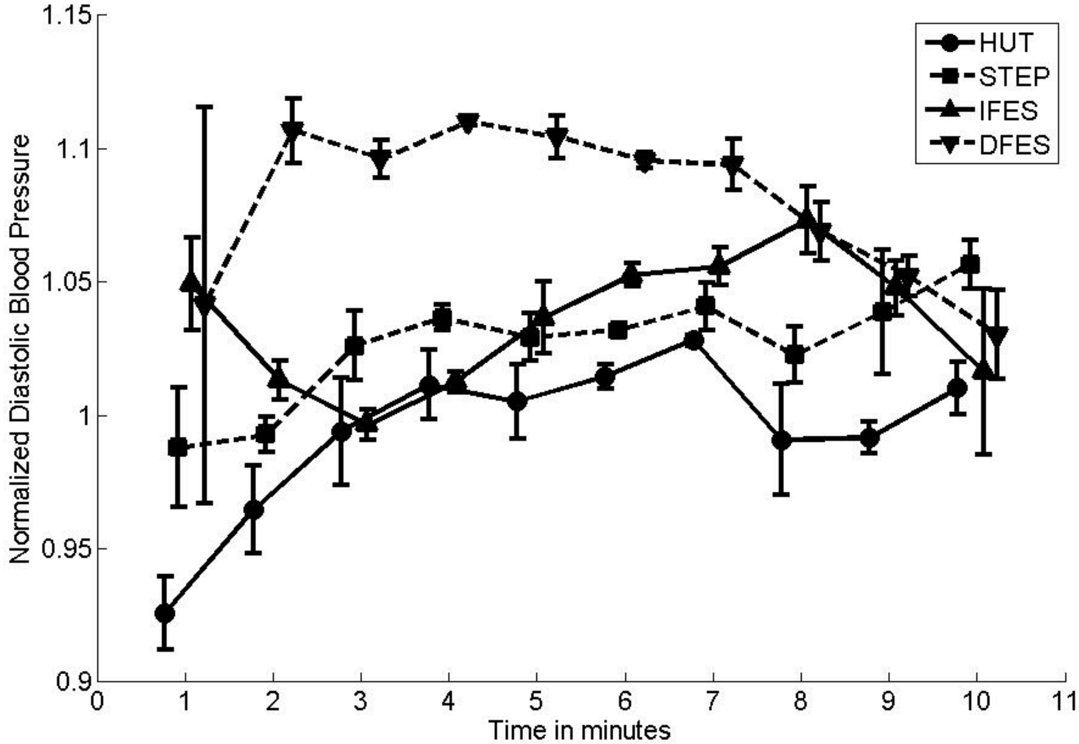

Figure 43: Normalized diastolic blood pressure for Participant BBAD. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

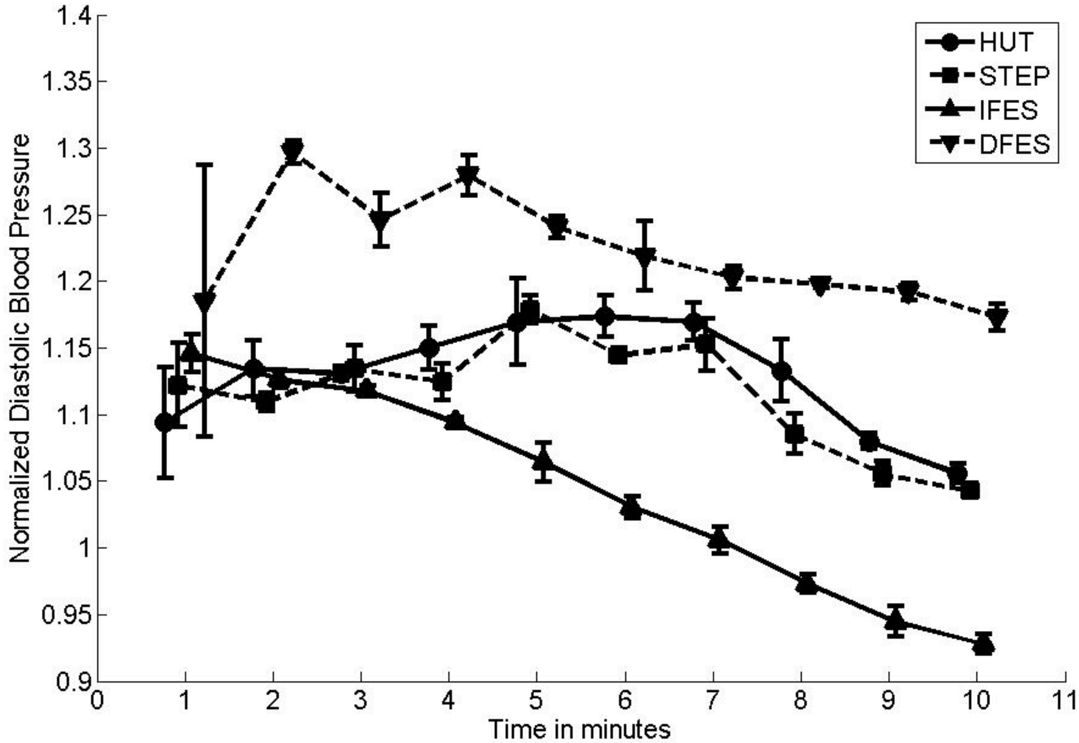

Figure 44: Normalized diastolic blood pressure for Participant BBAF. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

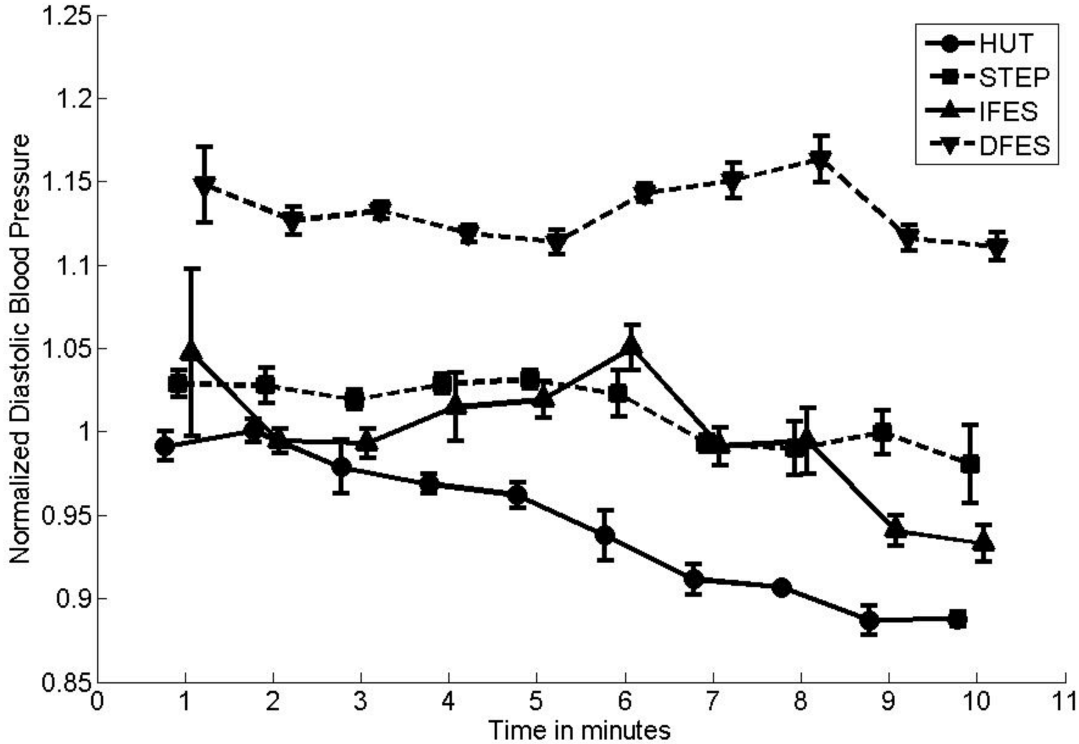

Figure 45: Normalized diastolic blood pressure for Participant BBAG. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Mean Blood Pressure

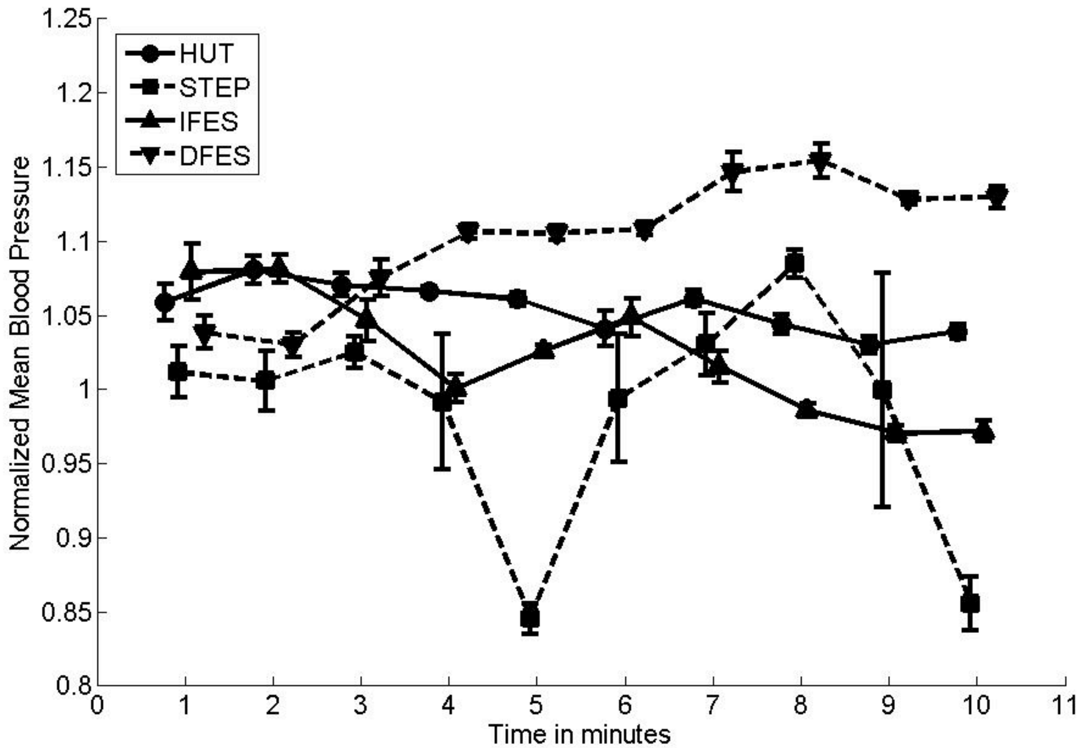

Figure 46: Normalized mean blood pressure for Participant BBAA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

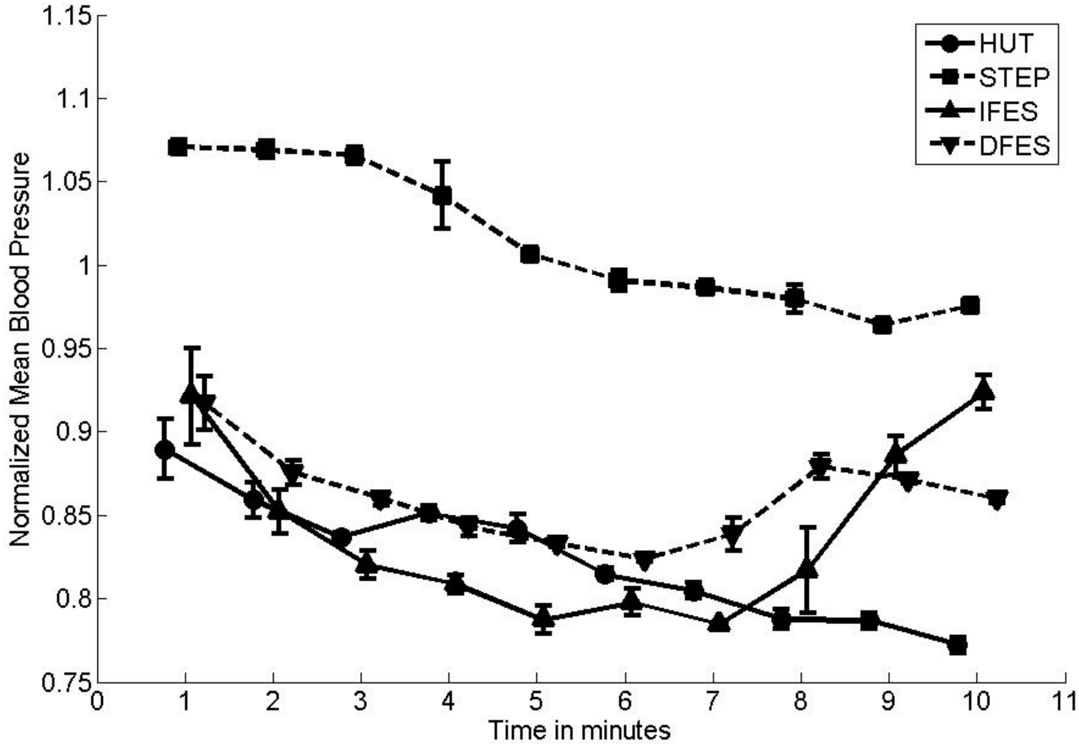

Figure 47: Normalized mean blood pressure for Participant BBAC. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

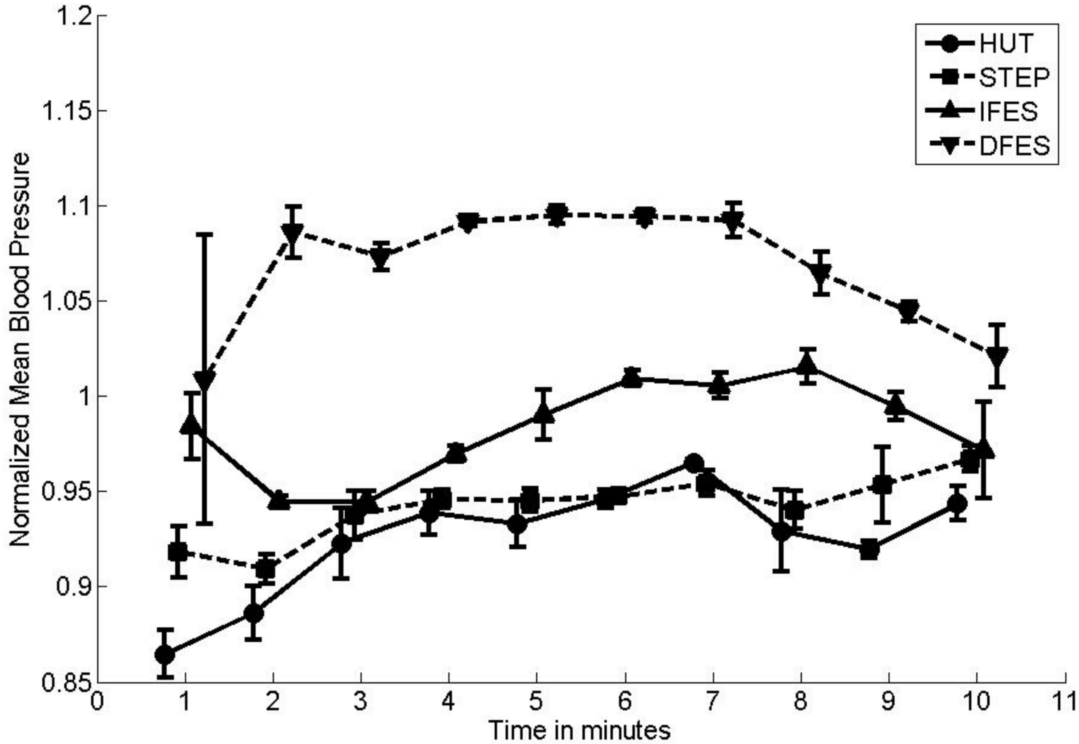

Figure 48: Normalized mean blood pressure for Participant BBAD. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

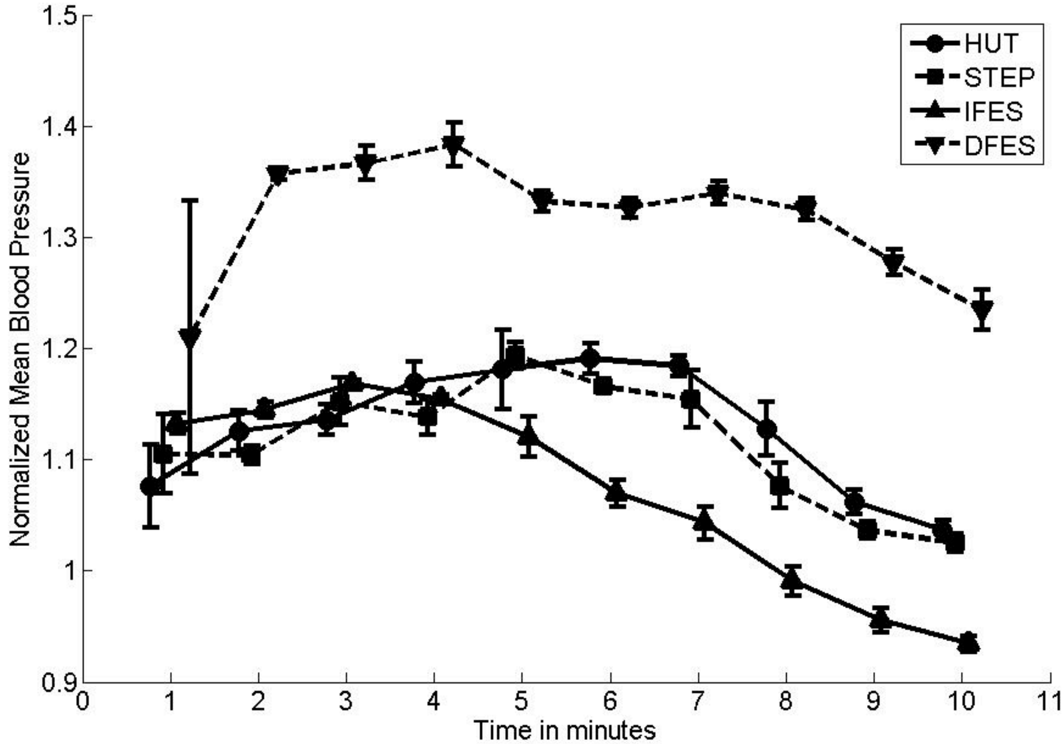

Figure 49: Normalized mean blood pressure for Participant BBAF. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

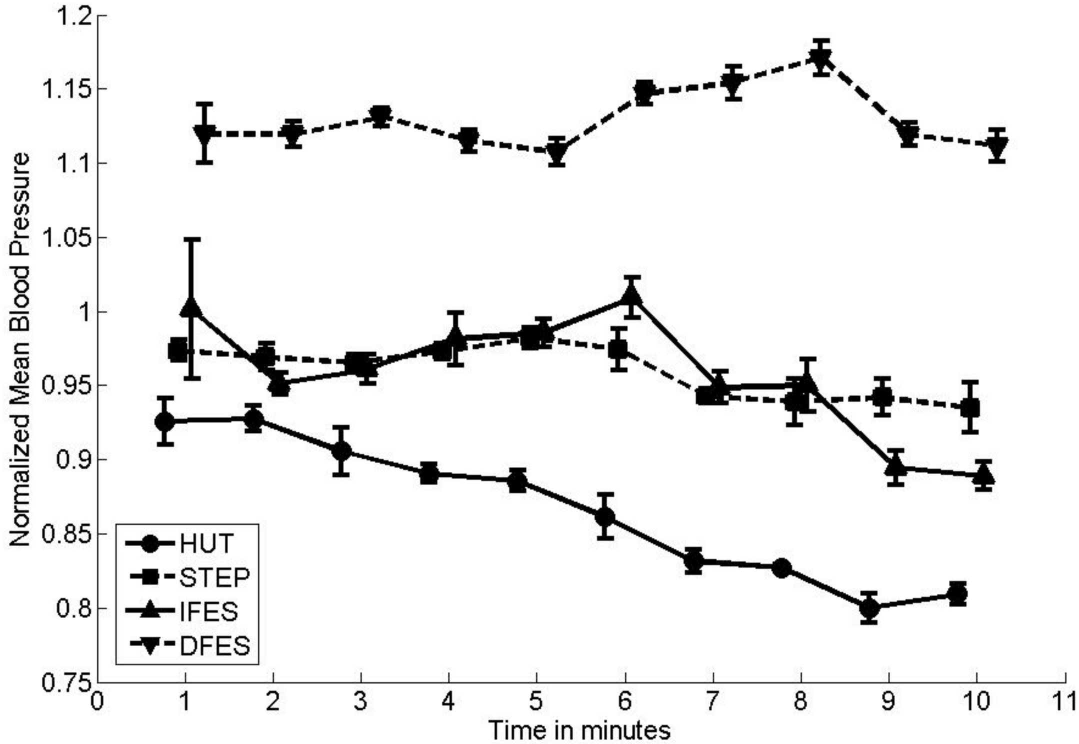

Figure 50: Normalized mean blood pressure for Participant BBAG. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Heart Rate

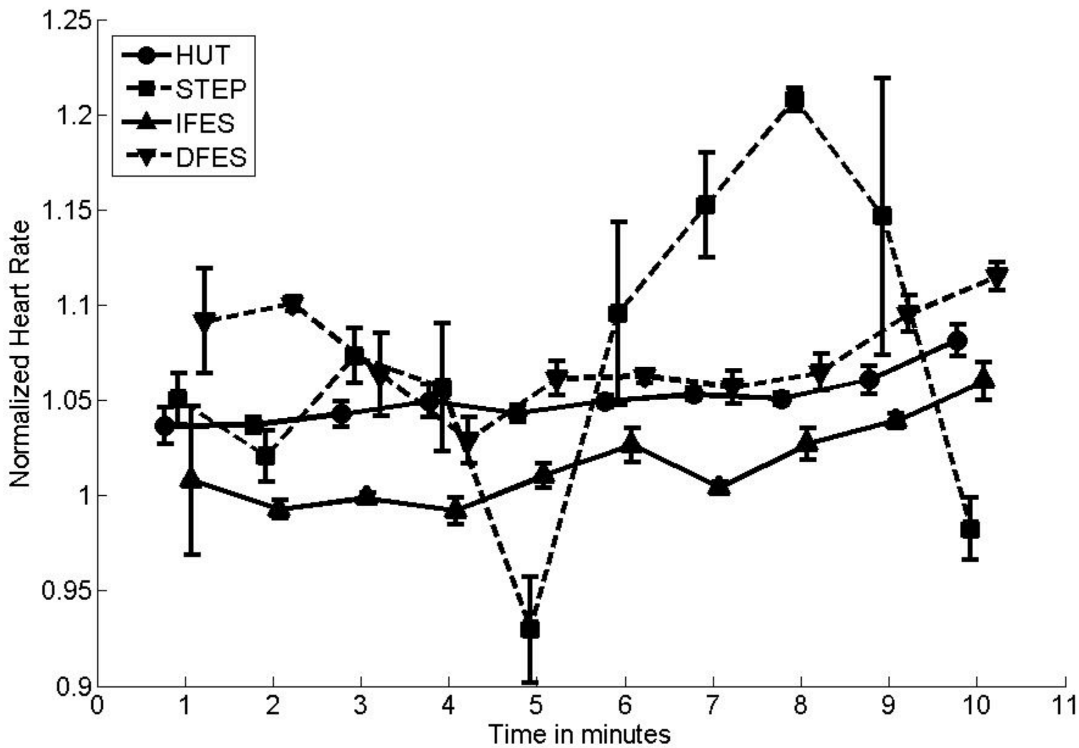

Figure 51: Normalized heart rate for Participant BBAA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

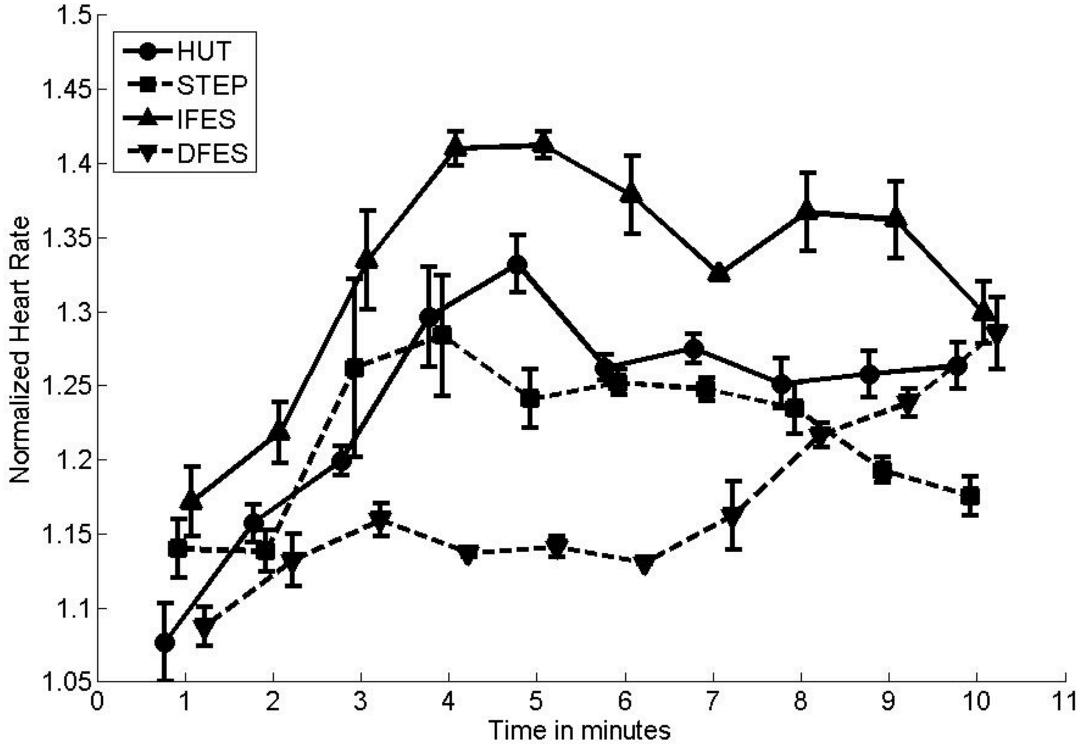

Figure 52: Normalized heart rate for Participant BBAC. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

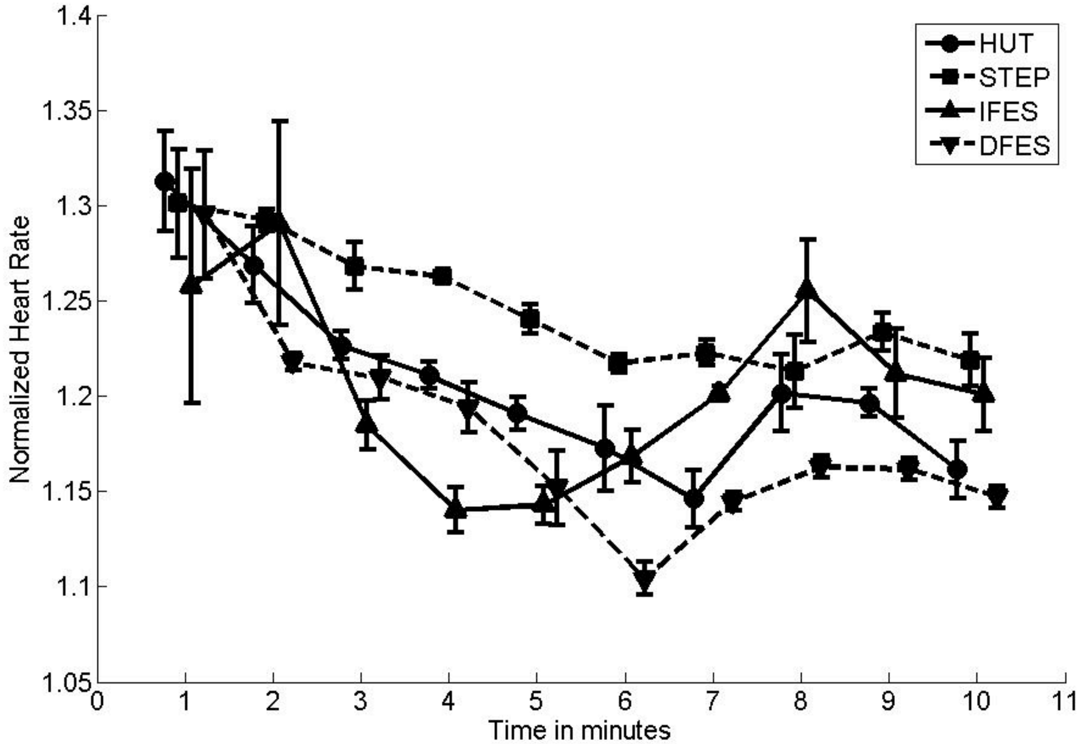

Figure 53: Normalized heart rate for Participant BBAD. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

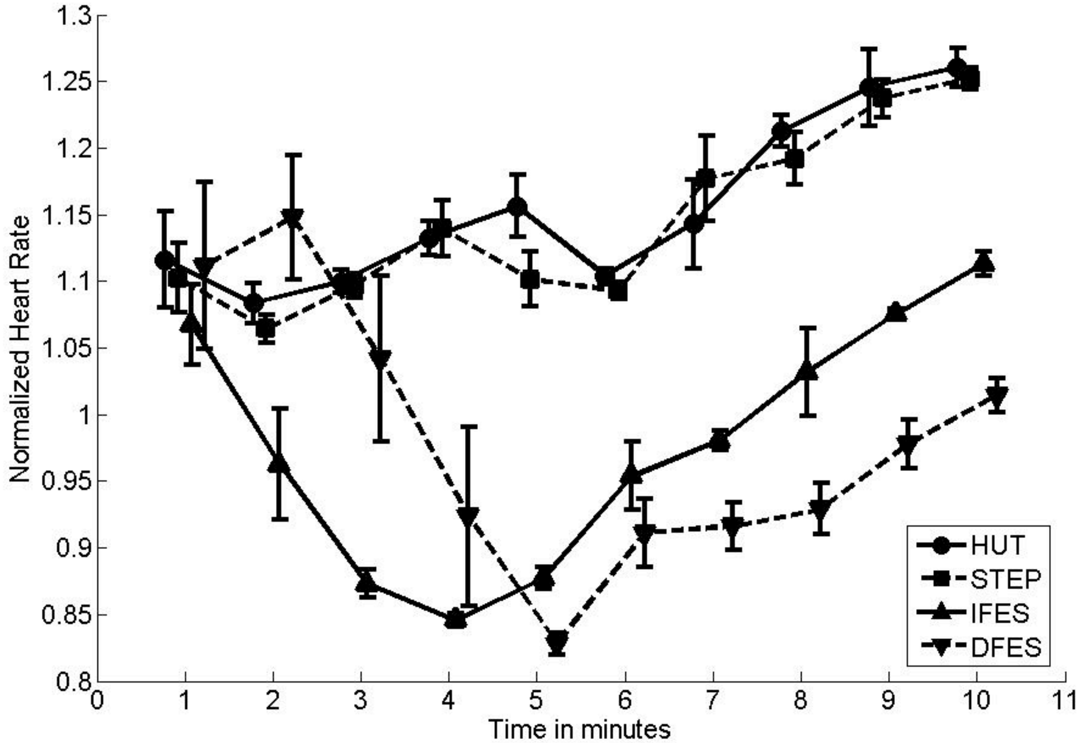

Figure 54: Normalized heart rate for Participant BBAF. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

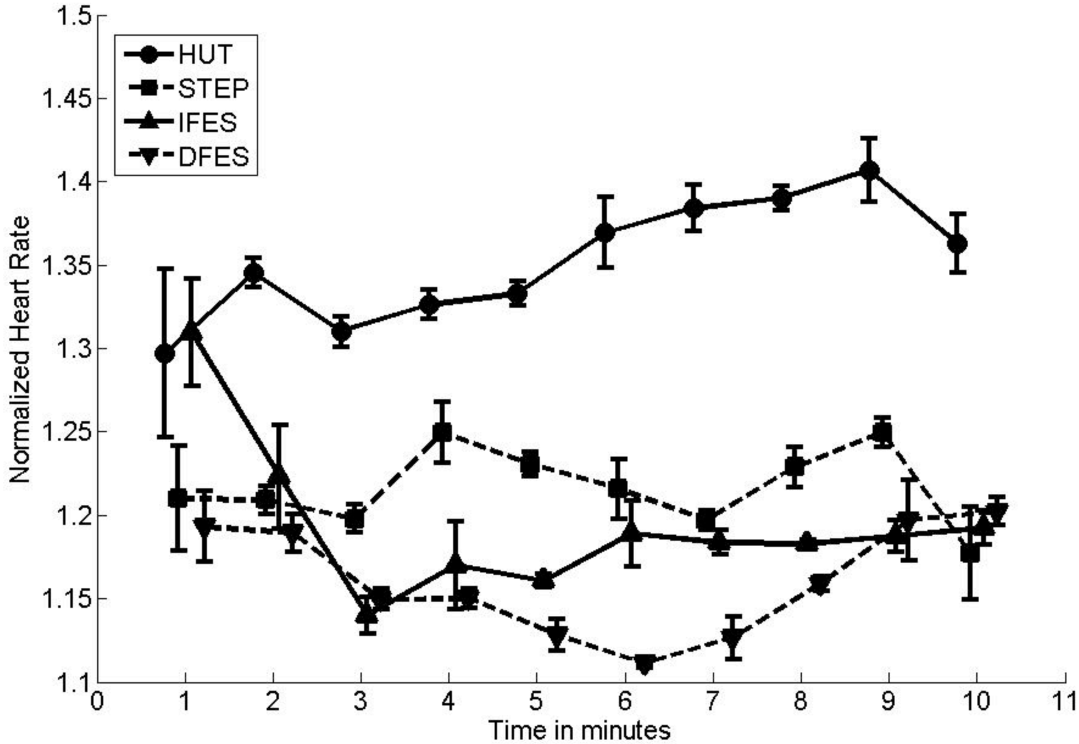

Figure 55: Normalized heart rate for Participant BBAG. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Stroke Volume

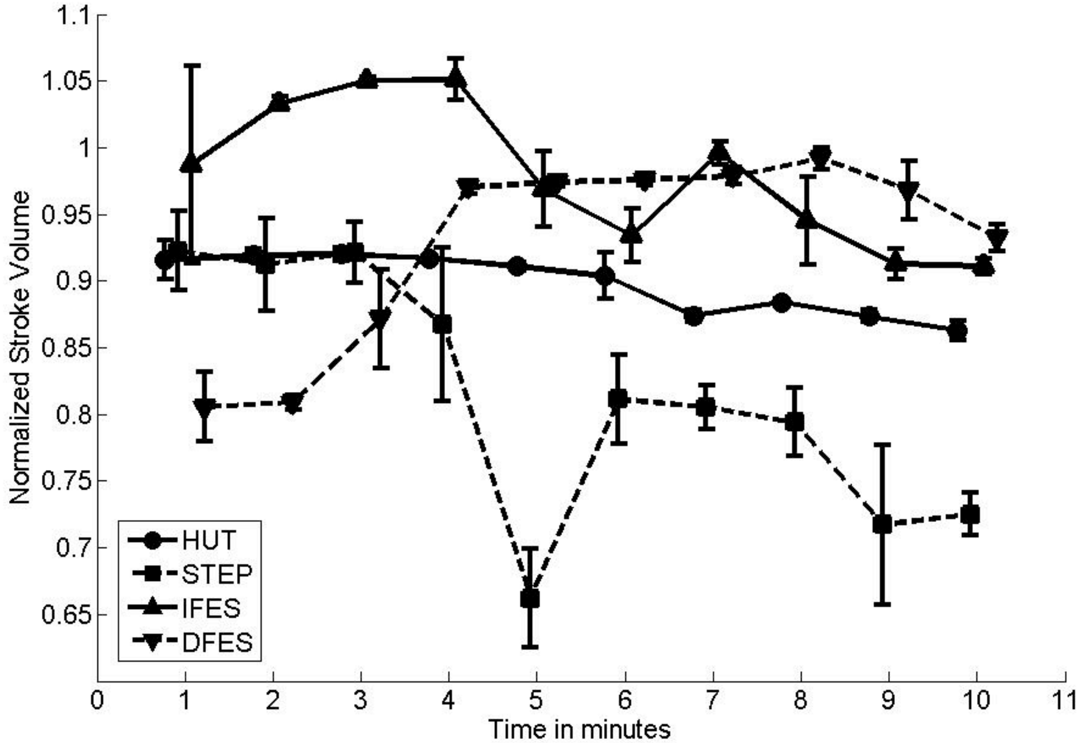

Figure 56: Normalized stroke volume for Participant BBAA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

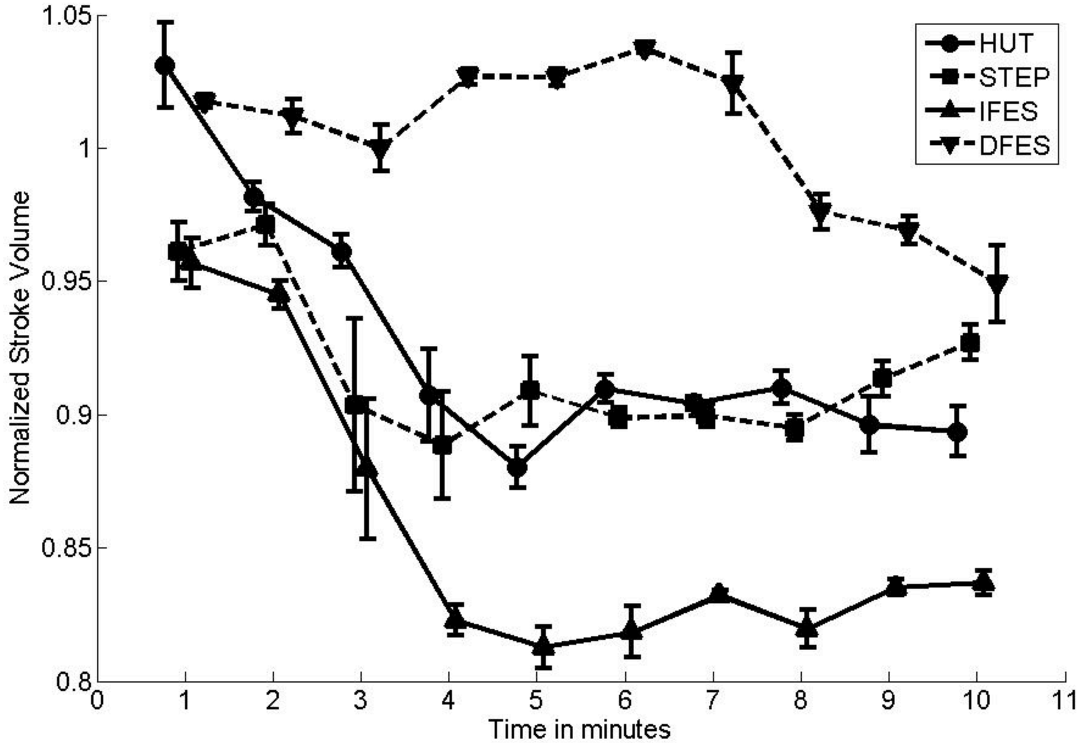

Figure 57: Normalized stroke volume for Participant BBAC. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

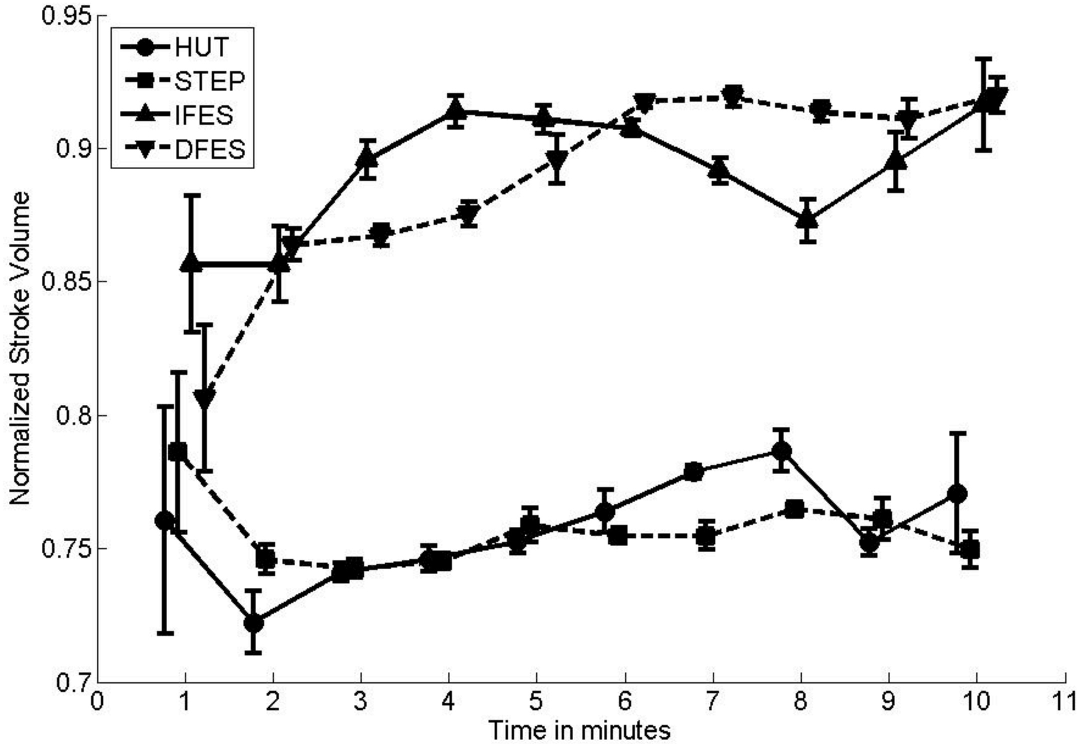

Figure 58: Normalized stroke volume for Participant BBAD. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

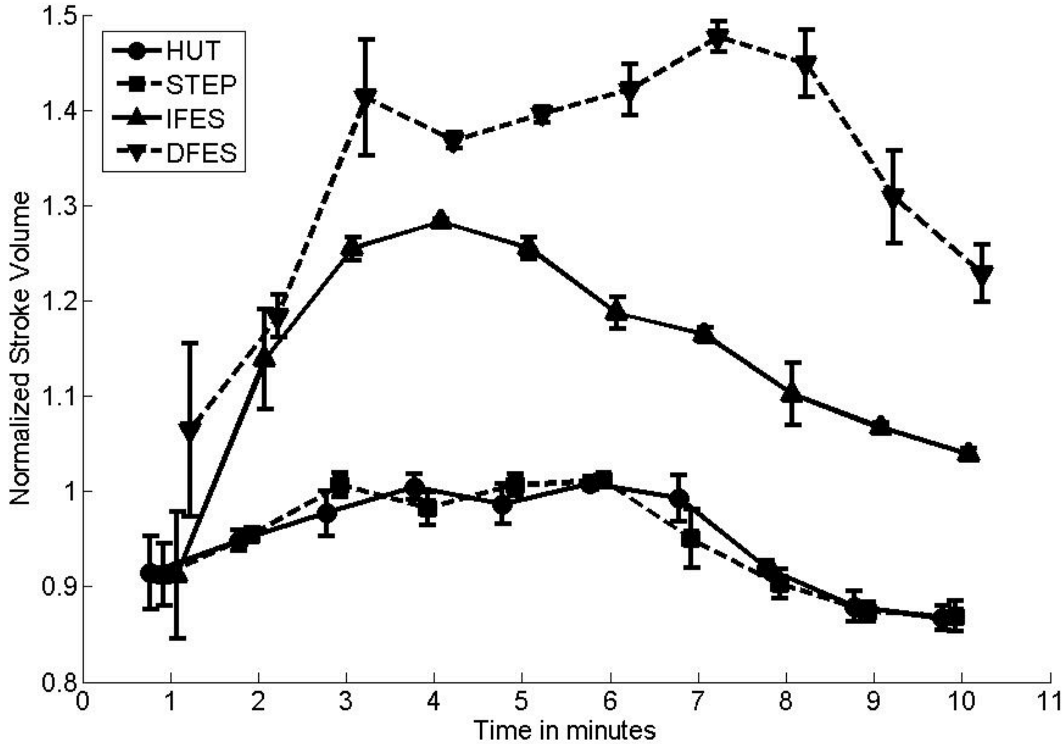

Figure 59: Normalized stroke volume for Participant BBAF. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

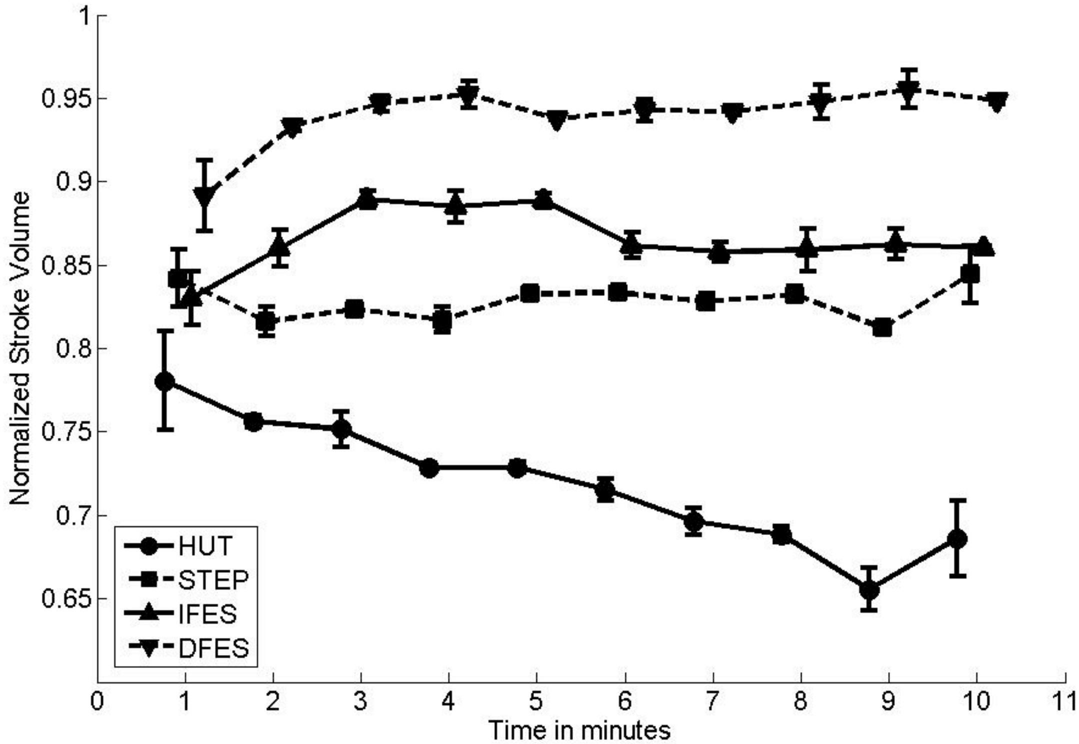

Figure 60: Normalized stroke volume for Participant BBAG. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

Systemic Vascular Resistance

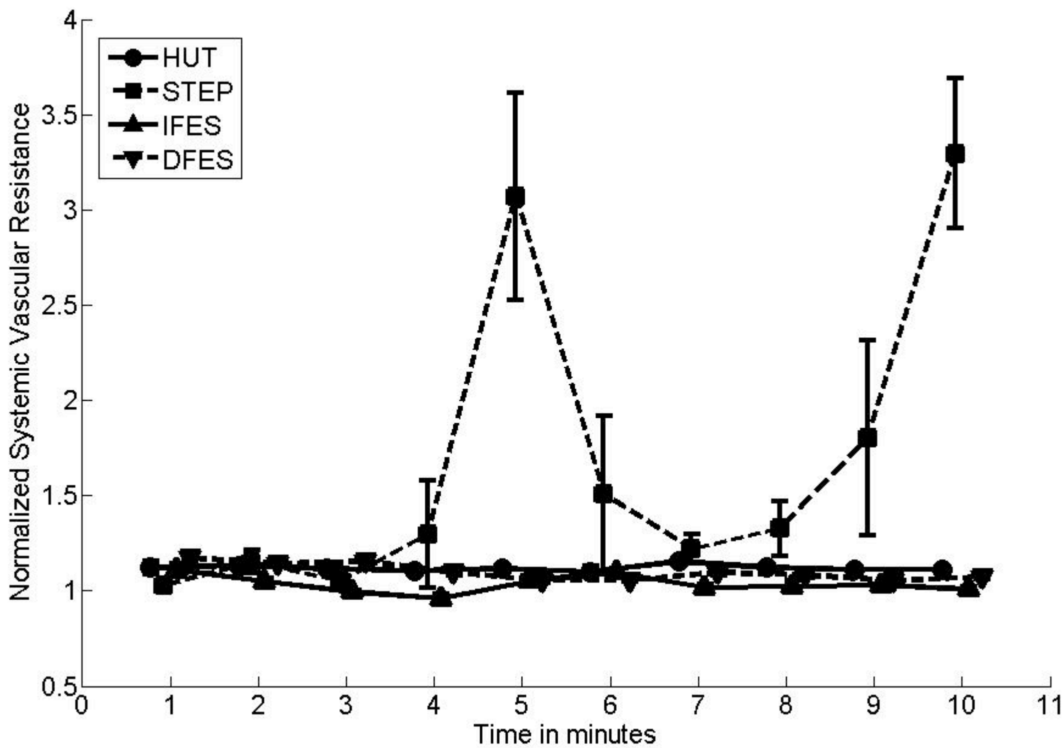

Figure 61: Normalized systemic vascular resistance for Participant BBAA. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

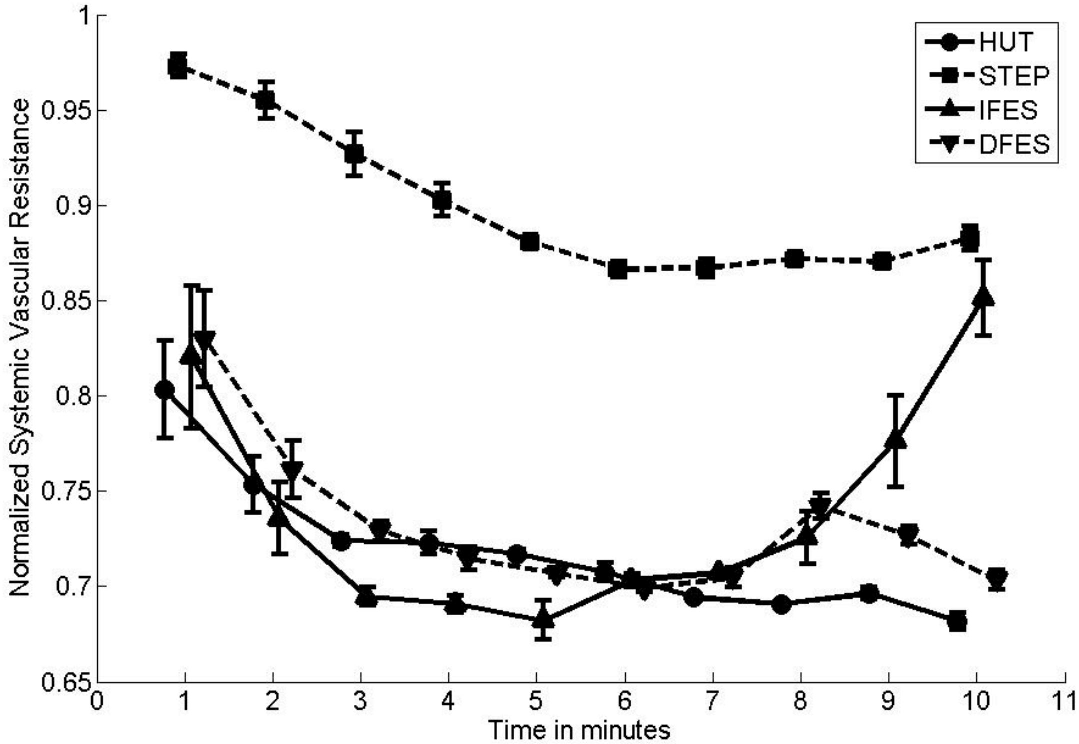

Figure 62: Normalized systemic vascular resistance for Participant BBAC. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

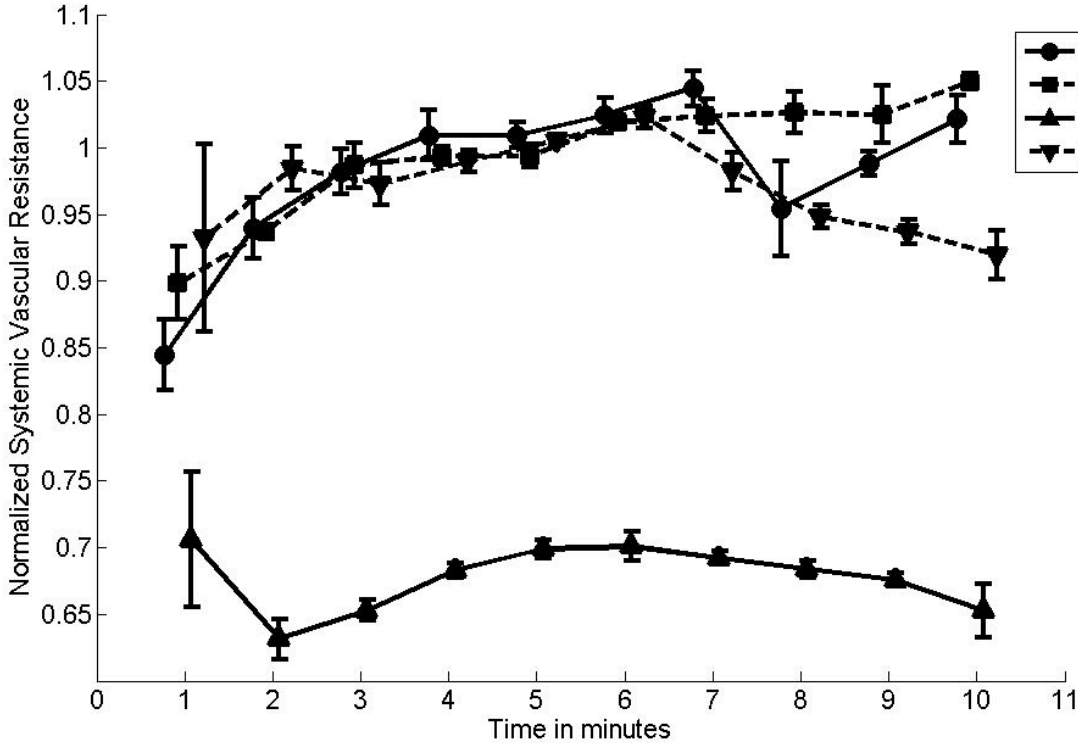

Figure 63: Normalized systemic vascular resistance for Participant BBAD. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

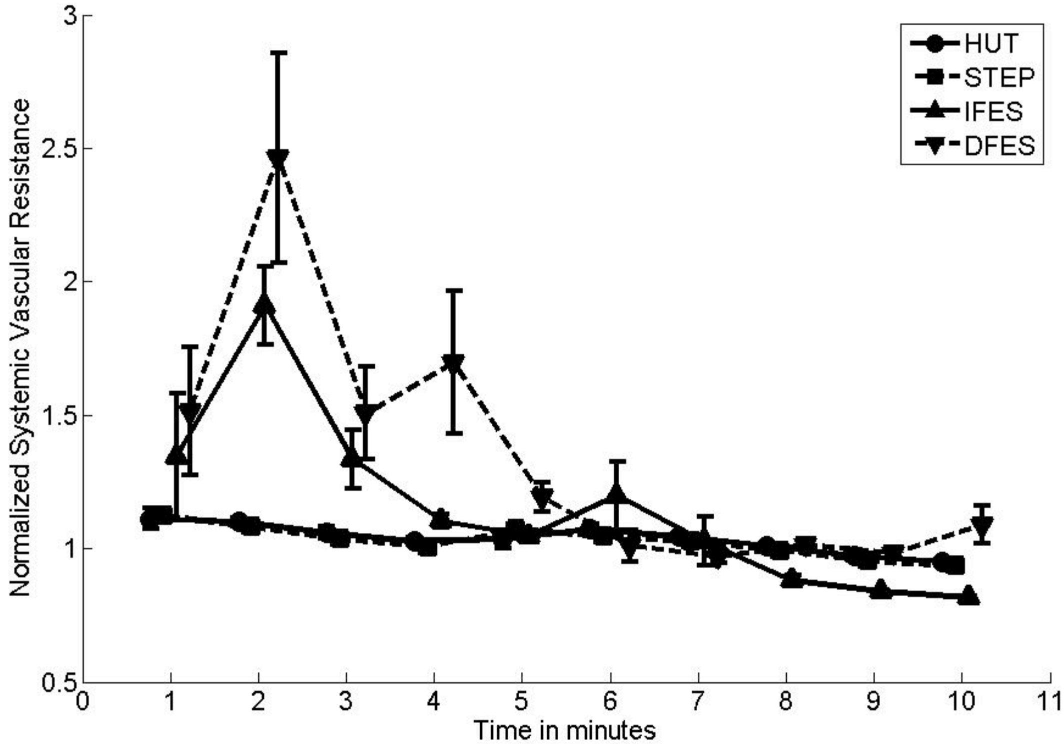

Figure 64: Normalized systemic vascular resistance for Participant BBAF. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.

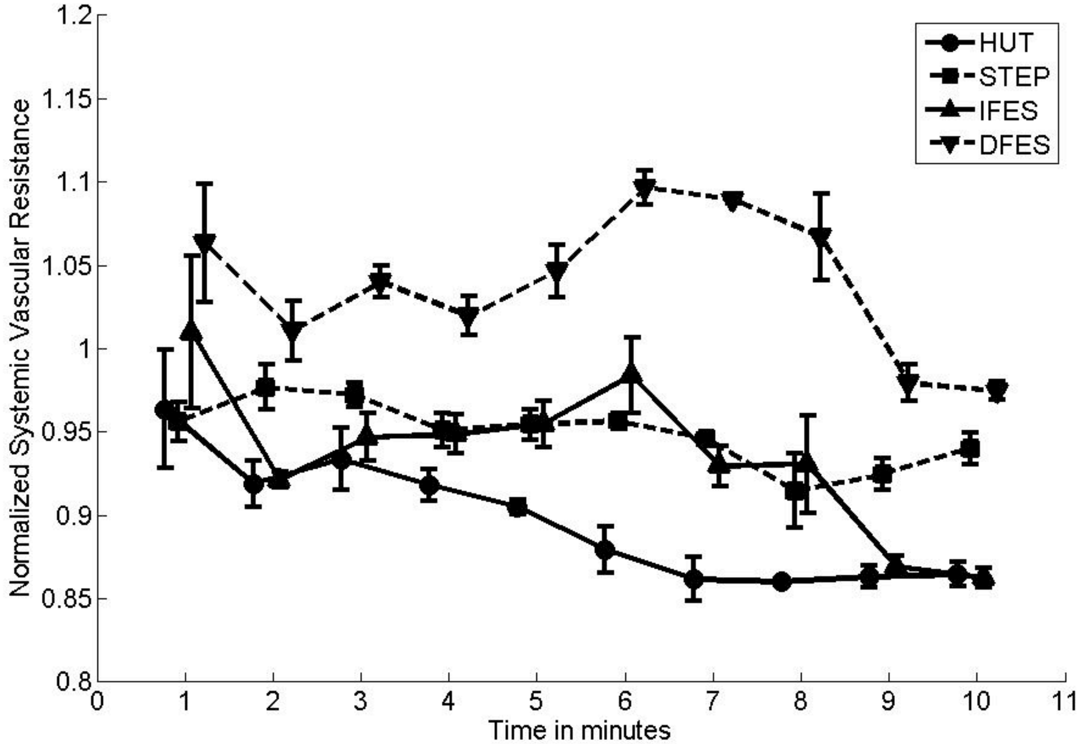

Figure 65: Normalized systemic vascular resistance for Participant BBAG. HUT represents head-up tilt without intervention, STEP represents imposed passive leg movements, IFES represents isometric FES, and DFES represents dynamic FES.