Cardiovascular Response of Individuals with Spinal Cord Injury to Dynamic Functional Electrical Stimulation under Orthostatic Stress

Takashi Yoshida, Kei Masani, Dimitry G. Sayenko, Masae Miyatani, Joseph A. Fisher, and Milos R. Popovic

Abstract—In this pilot study, we examined how effectively functional electrical stimulation (FES) and passive stepping mitigated orthostatic hypotension in participants with chronic spinal cord injury (SCI). While being tilted head-up to 70 degrees from the supine position, the participants underwent four 10-minute conditions in a random sequence: 1) no intervention, 2) passive stepping, 3) isometric FES of leg muscles, and 4) FES of leg muscles combined with passive stepping. We found that FES and passive stepping independently mitigated a decrease in stroke volume and helped to maintain the mean blood pressure. The effects of FES on stroke volume and mean blood pressure were greater than those of passive stepping. When combined, FES and passive stepping did not interfere with each other, but they also did not synergistically increase stroke volume or mean blood pressure. Thus, the present study suggests that FES delivered to lower limbs can be used in individuals with SCI to help them withstand orthostatic stress. Additional studies are needed to confirm whether this use of FES is applicable to a larger population of individuals with SCI.

Index Terms—Functional electrical stimulation, spinal cord injury, orthostatic hypotension, rehabilitation engineering.

I. INTRODUCTION

Orthostatic hypotension is a condition characterized by symptoms of cerebral hypoperfusion, such as headache, lightheadedness, and dizziness [1,2]. It occurs due to gravitational venous pooling and a subsequent decrease in the circulating blood volume. Most of the pooling occurs within ten seconds of standing up from the supine position; after three to five minutes, the pooling is almost complete [3]. The pooling reduces venous return and increases the intra-capillary pressure, which causes the fluid to escape into the interstitial space [3,4]. If a person continues to stand still, the arterial pressure may eventually decrease enough to cause hypoperfusion in the brain.

Normally, such orthostatic stress activates compensatory mechanisms that maintain arterial pressure. However, in individuals with spinal cord injury (SCI), impaired sympathetic cardiovascular control makes orthostatic hypotension more likely to occur. Furthermore, the symptoms of orthostatic hypotension can diminish mobility after SCI, especially in early stages of rehabilitation [5].

Pharmacological interventions against orthostatic hypotension use agents that either increase the sympathetic stimulation of the cardiovascular system or increase the blood volume in circulation, the latter of which is usually the first goal [6,7]. If an individual’s orthostatic tolerance does not improve after replenishing the circulating blood volume, the use of sympathomimetic agents may be considered [6]. Some sympathomimetic agents can cause undesirable side effects, such as tachycardia and hypertension, and some agents have not demonstrated efficacy with adequate sample sizes [6,7]. In any case, mitigating orthostatic hypotension with a pharmacological agent requires planning before a person is subjected to orthostatic stress.

Careful planning of pharmacological interventions should also consider concurrent non-pharmacological ones. Non-pharmacological interventions include increased salt and fluid intake to increase the circulatory volume, applying external compression to reduce venous pooling in the abdomen or the lower extremities, applying functional electrical stimulation (FES) on the lower extremity muscles to induce venous return, and exercising, either as training to improve orthostatic tolerance or as an intervention during orthostatic stress [7,8]. Among these interventions, FES is unique because it can generate dynamic muscle contractions in the legs, much like the skeletal muscle pump in able-bodied individuals. Also, the stimulation parameters can be customized easily and immediately to optimize the effect of FES. Thus, an intervention with FES is worth investigating.

Isometrically stimulating the leg muscles can help maintain arterial pressure of individuals with SCI during passive standing or graded tilting [9-12]. Our group has found that, in able-bodied individuals, applying FES with passive leg movements is even better for improving orthostatic tolerance [13]. Furthermore, the combined intervention of FES and passive leg movements most probably induces greater venous return than isometric FES [14]. The benefit of leg movements has been suggested by other studies, which showed that passive
or FES-induced leg cycling increased venous return or cardiac output in individuals with SCI [15-18]. To our knowledge, the combined effect of FES and passive leg movements on orthostatic hypotension has only been studied in able-bodied individuals. If we can achieve a similar synergy in individuals with SCI, FES intervention may become a viable means to treat orthostatic hypotension in this patient population.

We hypothesized that FES with passive leg movements should mitigate orthostatic hypotension in individuals with SCI by inducing venous return, thereby helping to maintain sufficient arterial pressure. Furthermore, we hypothesized that the combined intervention will be more effective than applying FES or passive leg movements separately. To test our hypothesis, we examined the cardiovascular responses of individuals with SCI during passive stepping and FES of the leg muscles (applied together or separately while the participants were tilted head-up to 70 degrees from the supine position).

II. MATERIALS AND METHODS

A. Participants

Ten individuals with chronic SCI participated in the experiment (TABLE I). Participants were recruited by convenience sampling from the population of outpatients at the Lyndhurst Centre of the Toronto Rehab. We approached all interested candidates with their consent, and their eligibility was determined by their physiatrists. As an inclusion criterion, the level of injury was specified as T6 or above. SCI at T6 or above would impair sympathetic vasoconstriction in the lower extremities [19]. Although SCI between T1 and T6 would leave some sympathetic stimulation of the heart intact, postural tachycardia does not protect individuals from orthostatic hypotension [20]. Also, without an increase in venous return, increased myocardial contraction would not be very effective in maintaining blood pressure. Thus, this criterion maximized the pool of potential participants while ensuring their predisposition to orthostatic hypotension. They did not have brittle diabetes, chronic renal failure, history of cardiovascular diseases, or peripheral nerve damage in the lower extremities. They were instructed not to consume caffeine, nicotine, or alcohol for eight hours before the experiment; they were also instructed not to consume fluids for two hours before the experiment. Seven participants consumed a light meal 2.6 ± 1.3 hours before the experiment. All experiments were conducted at a normal ambient temperature, between 9 a.m. and 5 p.m. Before the experiment, each participant gave written informed consent. The method of recruitment, the criteria for eligibility, and the experimental procedures were approved by the Research Ethics Board of the Toronto Rehabilitation Institute.

B. Protocol

Each participant underwent four experimental conditions: 1) passive head-up tilt (HUT) without any interventions, 2) passive stepping (STEP), 3) isometric FES (IFES), and 4) dynamic FES (DFES), which was a combination of FES and passive stepping. There were 24 possible sequences for applying four conditions without repetition. For each participant, a random sequence was selected using the random permutation function in a commercial numerical computing environment (MATLAB Version 7.10, The MathWorks Inc., USA). The 10-minute supine rest between each condition should have reduced any residual effects of the previous experimental condition to a negligible level [21, 22].

During each condition, participants were tilted head-up to 70 degrees from the supine position on a tilt table with a motorized stepper. This was done because 70-degree head-up tilt can frequently induce orthostatic hypotension in able-bodied individuals. Each condition lasted 10 minutes and was preceded by a 10 minutes of rest in the supine position. Tilting up before each condition took approximately 23 seconds, and tilting down after each condition took approximately 17 seconds. During the experiment, the participants were asked to report any symptoms of orthostatic hypotension, such as headache, dizziness, and lightheadedness. During the last minute of each condition, the inferior vena cava was imaged in the transverse plane. The electromyographic (EMG) signals of the leg muscles were recorded only during STEP because cyclic passive movements of the legs can induce rhythmic EMG activities. Throughout the experiment, beat-to-beat blood pressure was recorded non-invasively.

Tilt Table with a Motorized Stepper

We used a tilt table with a motorized stepper (Erigo, Hocoma AG, Switzerland). During STEP and DFES, the motorized mechanism of the table rotated the participants’ hips in the sagittal plane. The resulting movement was rhythmic stepping that alternated between the left and right legs at 40 steps (or 20 cycles) per minute. During the first 50% of a cycle, the hip was flexed by 20 degrees from the neutral position (neutral position being the one where the hip was straight). During the next 50% of a cycle, the hip was returned to the neutral position. For more details on the tilt table, refer to [23] and [24].
Functional Electrical Stimulation

FES was applied on four muscle groups: 1) the tibialis anterior, 2) hamstring, 3) quadriceps femoris, and 4) triceps surae muscles of both legs. We used current-regulated programmable transcutaneous FES systems (Compex Motion, Compex SA, Switzerland). The stimulation was bipolar and biphasic, with a maximum pulse width of 300 μs and stimulation frequency of 40 Hz. The frequency of 40 Hz was chosen to ensure tetanic contractions (i.e., continuous and smooth muscle contractions) without early fatigue [25].

To determine the stimulation amplitude, we measured the motor threshold and the maximum contraction amplitude for each muscle group. The threshold was measured as the lowest amplitude that induced a visually detectable or palpable muscle contraction. The maximum contraction amplitude was measured as the lowest amplitude to induce maximum contraction or as the maximum tolerable stimulation amplitude. During the experiment, the muscles were stimulated at 70% of the maximum contraction amplitude to ensure muscle contraction (TABLE II). If 70% of the maximum amplitude was less than the threshold, the threshold was used for stimulation.

Two surface electrodes (ValueTrode, Axelgaard Manufacturing Co., Ltd., USA) were placed on the proximal and distal ends of each muscle group. We used 5-cm-by-5-cm electrodes for the tibialis anterior and 5-cm-by-9-cm electrodes for other muscle groups. Conductive gel (Spectra 360 Electrode Gel, Parker Laboratories, Inc., USA) was applied on the interface between the skin and each electrode before securing the electrodes with surgical tapes.

During IFES, stimulation alternated between the thigh and shank muscles. During stimulation, the pulse width was linearly increased from 0 to 300 μs in 0.3 seconds, held constant for 0.9 seconds, and linearly decreased to 0 μs in 0.3 seconds. Then, the stimulation ceased for 0.9 seconds before increasing the pulse width again. The periods of stimulation and no stimulation were staggered so that 0.9 seconds of a constant pulse width coincided with 0.9 seconds of no stimulation between the thigh and shank muscles. Similar protocols had been used in studies that investigated the efficacy of isometric FES against orthostatic hypotension in individuals with SCI [9-12].

During DFES, each muscle group was stimulated while the muscles shortened from passive stepping. To estimate the dynamic length of each muscle group during stepping, we simulated the movement using a commercial simulation environment (Simulink Version 7.4 and SimMechanics Version 3.1.1, The MathWorks, Inc., USA). The lower extremity was modeled as a series of rigid bodies connected by rotational joints (i.e., hip, knee, and ankle), whose axes were perpendicular to the sagittal plane. Passive stepping was simulated as a multi-joint movement, with the foot rotating about a fixed axis (also perpendicular to the sagittal plane) near the toes, and the hip joint fixed to the inertial reference [23,24]. The simulation calculated the dynamic ankle, knee, and hip angles during passive stepping. Then, these angles were used to estimate the dynamic lengths of the leg muscles [26]. We estimated that the tibialis anterior and the quadriceps femoris would shorten while the hip rotated toward the neutral position. Conversely, the hamstring and triceps surae muscles would shorten during hip flexion. Therefore, during DFES, the tibialis anterior and quadriceps were stimulated while the hip rotated toward the neutral position (50% of a cycle), with the same linear increase, maintenance, and linear decrease of the pulse width as those of IFES. During hip flexion (50% of a cycle), they were not stimulated. The on-off pattern of stimulation was reversed for the hamstring and triceps surae muscles.

Blood Pressure Monitoring

We used a non-invasive cardiovascular monitoring system (Nexfin, BMeye B.V., Netherlands) that measured the beat-to-beat pressure in the finger artery via an inflatable cuff, which was worn by the participants over the intermediate phalanx bone of the right middle finger. Using the volume-clamp method [27,28] and the physiologic calibration algorithm [29], the monitoring system reconstructed beat-to-beat brachial pressure from the finger artery pressure. The brachial pressure was measured in millimeters of mercury (mmHg) and expressed as systolic, diastolic, and mean blood pressures. The system also calculated the heart rate in beats per minute, stroke volume in mL, and systemic vascular resistance in dyn·s/cm².

EMG Recording

We assessed the muscle activity of each muscle group during STEP to examine whether the induced stepping was purely passive or not. Surface EMG signals were recorded from the bellies of the medial gastrocnemius, tibialis anterior, biceps femoris, and rectus femoris during STEP (EMGSTEP) and during the supine rest (EMGREST). Before placing the electrodes, hair was removed using a razor. Then, light abrasion was applied to remove dead skin cells, and the abraded skin was cleansed using alcohol wipes. We used disposable Ag-AgCl surface electrodes (BiPole, Bortec Biomedical Ltd., Canada). Each electrode had a diameter of 10 mm and was placed in a bipolar configuration for each muscle, with a center-to-center electrode distance of 18 mm. The signals from the electrodes were amplified by 5,000 using an EMG measurement system (AMT-8, Bortec Biomedical Ltd., Canada) with a frequency response of 10 to 1,000 Hz. The analog output of the EMG measurement system and the phase signal of the motorized stepper were digitized at 2,000 Hz using a data acquisition system (PowerLab/12SP, ADInstruments, Australia).

Ultrasound Imaging of the Inferior Vena Cava

We assessed the intravascular circulatory blood flow by
measuring the cross-sectional area of the inferior vena cava (CSAIVC) with a diagnostic ultrasound system (ACUSON X150, Siemens AG, Germany). A transducer (CH5-2, Siemens AG, Germany) was placed on the subcostal area of the chest, approximately 2 cm inferior to the xiphoid process of the sternum. In this position, the inferior vena cava was viewed posteriorly to the liver at 5 MHz [14,30,31]. The same experimenter performed the ultrasound imaging for all participants. The video output of the ultrasound system was recorded onto the hard drive of a computer via a video capture device (Dazzle Video Creator Plus HD, Pinnacle Systems, USA) at 30 frames per second.

C. Data Analysis

The experimental data were processed in a commercial numerical computing environment (MATLAB Version 7.10, The MathWorks, Inc., USA) using a signal processing toolbox (Signal Processing Toolbox Version 6.13, The MathWorks, Inc., USA). Statistical analysis was performed using a statistics toolbox (Statistics Toolbox Version 7.3, The MathWorks, Inc., USA). The significance level for the statistical analysis was set to 5%.

Cardiovascular Responses

We conducted a series of statistical analyses using the binned differences (ΔSBP, ΔDBP, ΔMBP, ΔHR, ΔSV, and ΔSVR) of each participant (SBP is systolic blood pressure, DBP is diastolic blood pressure, MBP is mean blood pressure, HR is heart rate, SV is stroke volume, and SVR is systemic vascular resistance). First, baseline values were calculated as an average during the last minute of supine rest before each condition. Then, the cardiovascular parameters were binned by each minute of experimental conditions. Lastly, the binned parameters were expressed as a difference from the corresponding baseline value.

At each bin, we conducted two-tailed one-sample t-tests. The t-tests assessed if the cardiovascular parameters changed significantly from the baseline during experimental conditions.

To evaluate the effects of FES and passive stepping over time, we used three-way repeated-measures analysis of variance (ANOVA). The independent variables were 1) the presence or absence of FES in a condition, 2) the presence or absence of passive stepping in a condition, and 3) time (ten levels, one for each bin that represents each minute of an experimental condition).

To compare the cardiovascular responses between conditions, we conducted two-way repeated-measures ANOVA with Tukey’s HSD post hoc tests. The independent variables were 1) the type of experimental condition (four levels) and 2) time (ten levels).

To assess whether participants experienced orthostatic hypotension during any of the experimental conditions, we averaged systolic and diastolic blood pressures (separately) every ten heartbeats during the first three minutes of each condition. If systolic blood pressure decreased by 20 mmHg or more from the baseline, or if diastolic blood pressure decreased by 10 mmHg or more from the baseline, the decrease qualified as orthostatic hypotension [1,5]. No statistical analysis was performed with the number of episodes.

EMG Signals of the Leg Muscles

To evaluate whether EMGSTEP indicated muscle activity, we conducted paired t-tests for each muscle. We calculated the sum of squared frequency components between 10 and 250 Hz for unprocessed EMGSTEP and EMGREST. The sums excluded the frequency components between 59 and 61 Hz to eliminate the effect of electric hum. For each muscle, a paired t-test compared the group average of the sums between EMGSTEP and EMGREST.

Cross-sectional Area of the Inferior Vena Cava (CSAIVC)

CSAIVC was used as a surrogate measure of venous return. Due to the distensibility of the inferior vena cava, we assumed that CSAIVC would change in proportion to the venous volumetric flow into the right atrium [14]. This assumption is supported by the strong correlation between the diameter of the inferior vena cava and the central venous pressure in anesthetized individuals undergoing elective cardiac surgery [32,33].

Using image-processing software (ImageJ, National Institute of Health, USA), instantaneous CSAIVC was calculated by a blinded investigator, who did not know which experimental condition corresponded to each image sequence.

III. RESULTS

A. Cardiovascular Responses

Comparing Cardiovascular Responses to the Baseline

Fig. 1 shows the average responses of each cardiovascular parameter and the results of the t-tests. The letters, ‘H’, ‘S’, ‘I’, and ‘D’, which respectively represent HUT, STEP, IFES, and DFES, indicate that the corresponding value was significantly different from the baseline. Heart rate was significantly higher than the baseline at the majority of bins during HUT, STEP, and DFES. Systolic blood pressure decreased significantly during HUT and increased significantly during DFES, especially toward the end. Diastolic blood pressure increased significantly during STEP and DFES. Mean blood pressure increased significantly only during DFES. Stroke volume was significantly lower than the baseline throughout HUT and STEP. Systemic vascular resistance did not change significantly during any of the conditions.

Main Effects and Interactions of FES, Passive Stepping, and Time

The results of the three-way ANOVA are shown in TABLE III and TABLE IV. FES significantly affected ΔHR, ΔSBP, ΔMBP, and ΔSV (changes in heart rate, systolic and mean blood pressures, and stroke volume). On average, heart rate increased less with FES than without FES. Also, on average, systolic and
mean blood pressures increased more, and stroke volume decreased less with FES than without FES. Passive stepping significantly affected $\Delta$SBP, $\Delta$DBP, and $\Delta$MBP (changes in systolic, diastolic, and mean blood pressures): on average, systolic, diastolic, and mean blood pressures increased more with passive stepping than without it. Time did not independently affect any of the cardiovascular parameters. FES and passive stepping did not interact significantly. However, there was a significant interaction between FES and time for $\Delta$SBP and $\Delta$SV. Likewise, passive stepping and time interacted significantly for $\Delta$SBP, $\Delta$DBP, $\Delta$MBP, and $\Delta$SV.

Comparison between Experimental Conditions

TABLE V shows the results of the two-way ANOVA and post hoc tests with the cardiovascular parameters. There were significant differences between the conditions for all binned differences, except for $\Delta$SVR (change in systemic vascular resistance). Compared to the other three conditions, HUT resulted in higher $\Delta$HR and lower $\Delta$SBP, $\Delta$DBP, $\Delta$MBP, and $\Delta$SV. DFES had the highest $\Delta$SBP, $\Delta$DBP, and $\Delta$MBP. The

Fig. 1. Average cardiovascular responses. Positive values indicate an increased from the baseline. Error bars indicate the standard deviations between participants. □ represents HUT, ▽ represents STEP, ■ represents IFES, and ▼ represents DFES. The letters, ‘H’, ‘S’, ‘I’, and ‘D’, which respectively represent HUT, STEP, IFES, and DFES, indicate that the corresponding values were significantly different from the baseline. The line graphs have been staggered in the horizontal direction for better visualization. $\Delta$HR, $\Delta$SBP, $\Delta$DBP, $\Delta$MBP, $\Delta$SV, and $\Delta$SVR are changes in heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure, stroke volume, and systemic vascular resistance, respectively. BPM is beats per minute.
mean cardiovascular parameters during each experimental condition can be compared in TABLE VI.

**Observed Episodes of Orthostatic Hypotension**

Based on the changes in blood pressure alone, we determined the number of participants that experienced orthostatic hypotension during the experiments: 6 during HUT, 5 during STEP, 4 during IFES, and 3 during DFES. Despite these findings, none of the participants reported perceived symptoms of orthostatic hypotension during the experiments.

**B. EMG Signals of the Leg Muscles**

The paired t-test failed to reject the null hypothesis for all muscles. In other words, for all muscles, the spectral power of EMGSTEP did not significantly differ from that of EMGREST muscles. In other words, for all muscles, the spectral power of EMGSTEP did not significantly differ from that of EMGREST muscles. In other words, for all muscles, the spectral power of EMGSTEP did not significantly differ from that of EMGREST muscles. In other words, for all muscles, the spectral power of EMGSTEP did not significantly differ from that of EMGREST muscles. In other words, for all muscles, the spectral power of EMGSTEP did not significantly differ from that of EMGREST muscles.

**C. Cross-sectional Area of the Inferior Vena Cava (CSAIVC)**

Ultrasound imaging was successfully completed for 4 participants (A, C, D, and I). For the remaining 6 participants, the inferior vena cava could not be located while the participants were in the tilted position. Of the 4 participants, images for 2 participants (D and I) were clear enough to warrant further analysis.

For participant D, 53.9% of the images from HUT, 43.3% of the images from STEP, and 40.9% of the images from IFES could not be analyzed due to poor quality. Likewise, 25.4% of the images from HUT, 30.3% of the images from IFES, and 41.3% of the images from DFES could not be analyzed for participant I. Based on the high percentages of images with poor quality, we did not conduct further analysis. Therefore, subsequent discussions regarding the images from HUT, 25.4% of the images from STEP, 30.3% of the images from IFES, and 41.3% of the images from DFES could not be analyzed for participant I. Based on the high percentages of images with poor quality, we did not conduct further analysis. Therefore, subsequent discussions regarding

<table>
<thead>
<tr>
<th>Cardiopulmonary parameter</th>
<th>FES</th>
<th>Passive stepping</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 88</td>
<td>0.026</td>
<td>0.089</td>
<td>0.772</td>
</tr>
<tr>
<td>SBP 12.5</td>
<td>0.004</td>
<td>0.009</td>
<td>0.607</td>
</tr>
<tr>
<td>DBP 3.34</td>
<td>0.101</td>
<td>0.0182</td>
<td>0.648</td>
</tr>
<tr>
<td>MBP 12.5</td>
<td>0.006</td>
<td>0.0102</td>
<td>0.498</td>
</tr>
<tr>
<td>SV 15.6</td>
<td>0.003</td>
<td>0.159</td>
<td>1.59</td>
</tr>
</tbody>
</table>

**IV. DISCUSSION**

**A. Cardiovascular Responses**

Our results demonstrated that FES and passive stepping significantly affected the cardiovascular responses during a head-up tilt. During conditions with FES (i.e., IFES and DFES), on average, heart rate increased less, systolic and mean blood pressures increased more, and stroke volume decreased less (Fig. 1, TABLE III). During conditions with passive stepping (i.e., STEP and DFES), on average, systolic, diastolic, and mean blood pressures increased more (Fig. 1, TABLE III). These results imply that FES and passive stepping independently increased blood pressure, but FES also mitigated tachycardia and a decrease in stroke volume.

As TABLE IV shows, we found significant interactions between FES and time for ∆SBP and ∆SV (changes in systolic blood pressure and stroke volume, respectively) and between passive stepping and time for ∆SBP, ∆DBP, ∆MBP, and ∆SV (changes in systolic, diastolic, and mean blood pressures, and stroke volume, respectively). These interactions probably indicate that the effects of FES and passive stepping on the respective binned differences became more pronounced over time (Fig. 1).

There was no significant interaction between FES and passive stepping (TABLE IV), implying that the combined effect of FES and passive stepping was not synergistic. This was contrary to our expectation that DFES would induce greater venous return than IFES alone by contracting the leg muscles in a more physiologically correct manner. Although passive stepping and FES independently mitigated a decrease in stroke volume (Fig. 1), they did not combine synergistically or even additively as DFES. The lack of synergy may have been caused by a ceiling effect.

We found differences in cardiovascular responses between the conditions. Without any intervention (i.e., during HUT), heart rate significantly increased from the baseline and stroke volume significantly decreased from the baseline (Fig. 1). The increase in heart rate was probably due to reduced parasympathetic stimulation of the heart, and the decrease in
or STEP: during IFES and DFES, stroke volume did not significantly decrease from the baseline most of the time (Fig. 1), and ΔSV (change in stroke volume) was significantly greater during IFES and DFES than during HUT or STEP (TABLE V). These results suggest that IFES and DFES induced greater venous return than STEP. Despite the common effect on venous return, IFES and DFES affected blood pressure differently. IFES maintained blood pressure as effectively as STEP (Fig. 1, TABLE V), whereas DFES resulted in significantly higher ΔSBP, ΔDBP, and ΔMBP (changes in systolic, diastolic, and mean blood pressures, respectively) than the other conditions (TABLE V). Also, blood pressure was significantly higher than the baseline during most of DFES (Fig. 1). Among the determinants of blood pressure (i.e., heart rate, stroke volume, and systemic vascular resistance), only ΔHR (change in heart rate) was significantly greater during DFES than during IFES (TABLE V). This discrepancy is partially explained by the perception of exertion (i.e., the perceived intensity of exercise) [36]. Because DFES involved passive leg movements, the participants may have perceived greater exertion during DFES. This could have reduced the parasympathetic stimulation of the heart and contributed to greater ΔHR, which increased the blood pressure (Fig. 1). The observed differences between DFES and IFES for changes in blood pressure suggest that DFES may be a more effective intervention against orthostatic hypotension. However, further investigation is required to confirm the relative efficacy of DFES and IFES.

In our previous study [14], the combined intervention of FES and passive stepping (DFES) maintained venous return much more effectively than IFES alone. In the present study, IFES and DFES did not significantly differ in their ability to induce venous return: ΔSV (change in stroke volume) did not differ significantly (TABLE V). This difference between our results and the previous findings may be due to discrepancies in methods. Several discrepancies in methods suggest that IFES in [14] may have been less effective compared to IFES in the present study. First, in [14], the gastrocnemius and quadriceps femoris were stimulated simultaneously during one half of a cycle, and the hamstring was stimulated during the other half. This pattern may not have created the squeezing effect that we intended with the protocol in the present study. Second, not stimulating the tibialis anterior would have reduced the number of veins compressed during contractions in [14]. Third, [14] used lower stimulation intensities. Although the observed difference between the two studies can be attributed to the above methodological discrepancies, further studies are needed to properly explain the difference.

### B. EMG Signals of Leg Muscles

Passive leg movements in an upright standing position can induce rhythmic EMG signals in individuals with SCI [37]. These signals can have comparable amplitudes to those of able-bodied individuals during locomotion [38,39], and the signals are associated with observable changes in the oxygenation of the paralyzed muscles [40]. In this study, we...
examined if passive stepping during STEP induced similar muscle activities that could have increased venous return.

The frequency analysis indicated that EMG signals during STEP were insignificant. We speculate that the lack of hip extension, insufficient weight bearing, and the slower rate of stepping caused the discrepancy between our results and the previously reported rhythmic EMG signals [37]. Passive stepping that we applied did not include hip extension, whereas the study that reported rhythmic EMG signals applied approximately 14 degrees of hip extension [37]. Our participants supported approximately 7.5 to 24% of their body weight on each foot, varying within each cycle; in the study that measured rhythmic EMG signals, the participants supported almost their entire body weight on the soles [37]. Lastly, we applied stepping at 20 cycles per minute, whereas rhythmic EMG signals were recorded at 60 cycles per minute [37].

The measured EMG signals suggested that passive stepping did not cause significant muscle activation. Therefore, STEP probably mitigated the decrease in stroke volume by stretching the veins, whose one-way valves caused venous return when the diameter of the veins decreased due to stretching.

C. Cross-sectional Area of the Inferior Vena Cava (CSAIVC)

Although we used the same experimenter and technique as in the previous study [14], we could not measure CSAIVC with sufficient accuracy due to poor image quality. Based on the body mass index, the majority of our participants were overweight or obese (which is common after SCI), whereas none of the participants in [14] was overweight. This may have been partially responsible for our inability to measure CSAIVC. Though not an independent determinant, obesity is strongly associated with poor image quality in ultrasonography, primarily due to an inadequate acoustic window for the region of interest [41]. Also, if two abdominal walls have the same muscle thickness, the one with a greater fat composition reduces the mean grey level and contrast more [42]. Further consideration is required before measuring CSAIVC in future studies with SCI individuals.

D. Limitations of the Study

The present pilot study demonstrates the feasibility of using FES to mitigate orthostatic hypotension in individuals with SCI. However, the heterogeneity of our participants implies that larger-scale studies are needed to prove that this use of FES applies to the general SCI population. Although heterogeneity is common in any given local population of individuals with SCI, future studies should better control the extent of preservation of autonomic function. Using only the AIS classification, level of injury, and post-injury durations may be inadequate for assessing the preservation of autonomic function: the framework for a more appropriate assessment is described in [19]. With properly stratified participants, we can conduct more rigorous studies that will better explain how interventions like IFES, DFES, and STEP differently affect the orthostatic tolerance of individuals with SCI. For now, we conclude that cyclic FES to the leg muscles can effectively induce venous return, thereby helping to maintain the blood pressure of individuals with SCI under orthostatic stress.

E. Research towards Clinical Implementation

As stated above, this pilot study suggests that FES might enable individuals with SCI to withstand orthostatic stress for a prolonged period. If FES is successfully implemented, individuals with SCI may be allowed to receive treatments that are otherwise precluded due to orthostatic stress. This would be beneficial especially in early rehabilitation because patients would not have to merely wait for their blood pressure regulation to recover, and earlier rehabilitation will prevent prolonged inactivity and subsequent secondary complications such as muscle atrophy, pressure ulcers, and demineralization of the lower limb bones. For example, there are many potential clinical benefits of weight bearing in a standing position for individuals with SCI. Such weight bearing can mitigate hypercalciuria [43,44] and a decrease in bone mineral density [45]. It may also help to prevent urinary tract infections by increasing the bladder pressure [46]. Individuals with SCI have reported that standing (either passively or with assistive devices) improved many aspects of their health, including the perception of well-being, circulation (e.g., reduced swelling in the lower extremities), reflex activity (e.g., reduced muscle spasms), and bowel and bladder function [47]. By applying the FES intervention that this study presented, we may be able to place people with SCI in a standing posture with a mitigated risk of orthostatic hypotension. The FES intervention can also mitigate this risk during reaching, grasping, and trunk balance exercises.

Despite the potential benefit, additional investigation is required before FES can be implemented in a clinical setting. Specifically, we need to investigate whether a combination of FES and passive stepping can be improved to provide better outcomes than FES alone. The findings of such investigation will help us identify the best intervention against orthostatic hypotension in individuals with SCI.

V. Conclusion

Orthostatic hypotension occurs if venous pooling due to a postural change is not adequately counteracted by reflexive sympathetic cardiovascular stimulation. The present study suggests that, during a 70-degree head-up tilt, individuals with SCI at T6 or higher can better maintain their blood pressure if FES is applied cyclically to their leg muscles. FES achieves this function by inducing venous return. Passive stepping can also induce venous return, but it is less effective than FES. Consequently, passive stepping is less effective in mitigating a decrease in arterial pressure during a 70-degree head-up tilt. Thus, FES appears to be more effective than passive stepping as an intervention against orthostatic hypotension in individuals with SCI. When passive stepping was combined with FES, they
did not interfere with each other, but they also did not interact synergistically.

ACKNOWLEDGMENT

Authors thank Diane Kostka for analyzing the ultrasound images. Funding for this study was provided by the Natural Sciences and Engineering Research Council of Canada (Grant #249669), the Toronto Rehabilitation Institute, Ontario Ministry of Health and Long-Term Care, and HOCOMA AG, which supported the EMG measurements and analysis pertinent to this study.

REFERENCES


