Targeted Transcutaneous Stimulation to Restore Autonomic Cardiovascular Health in Veterans with Spinal Cord Injury

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Abstract:

Recent evidence indicates that increased arterial stiffness is an independent predictor of cardiovascular disease risk, which may contribute to the heightened cardiovascular morbidity and mortality in the spinal cord injury (SCI), compared to general, population. Increased reliance on the renin-angiotensin-aldosterone system (RAAS) is believed to mitigate orthostatic falls in blood pressure (BP) and reduce the severity of symptoms reporting; however, findings in the general population link the RAAS with vascular restructuring and remodeling. Therefore, clinical intervention to stabilize and normalize BP should be a priority in hypotensive individuals with SCI. Advances in methods of neuromodulation of the spinal processes offer a non-pharmacologic approach to restore endogenous autonomic cardiovascular control and improve orthostatic BP control. Based on our present understanding of the somatovisceral integration within the spinal cord, it is plausible that transcutaneous spinal cord stimulation (TSCS) can be targeted to excite and modulate appropriate spinal autonomic circuitry to rapidly normalize orthostatic BP; however, electrode placement and stimulation parameter mapping is needed to optimize orthostatic BP control. Therefore, our primary aim is to identify an individualized map using noninvasive TSCS of the spinal autonomic circuitry that results in an increase of seated BP. Our secondary aim is to compare BP, cerebral blood flow velocity (CBFv), plasma concentrations of norepinephrine, renin and aldosterone during a head-up tilt with and without optimal TSCS. Participants will go through a screening process to determine if participant experiences orthostatic hypotension. 12 participants who are cleared, will go through multiple mapping sessions to find out the most appropriate electrode placement to increase BP and then will perform an orthostatic provocation on a tilt table during stimulation to determine differences with stim and without.

Objective: To identify an individualized map of the spinal autonomic circuitry that results in an increase of seated BP using noninvasive TSCS.

Hypotheses:

1. We hypothesize that electrode placement at the lower thoracic (T7/8) and 50 mA current will be the optimal parameters to increase cardiovascular function.
2. We hypothesize that seated systolic BP will significantly increase following optimal TSCS.

Review of Literature:

Approximately 17,700 new cases of spinal cord injury (SCI) occur in the United States each year (1) and the Veterans Affair (VA) provides care for approximately 26% of Americans with SCI, making it the single largest network of care for persons with SCI (2). The health care costs for Veterans with SCI are 6.5 times greater than the average veteran (2), and although improvements in post-injury care have contributed to extended life expectancies in the SCI population, longevity remains below the general population, due, in part, to an increased incidence of cardiovascular disease (CVD), which is a leading cause of mortality in individuals with chronic SCI (3). In 2013, a study completed retrospectively in 147 Veterans with SCI, demonstrated that those who survived the initial two years post-injury, are at increased risk of pre-mature coronary artery disease compared to the general population (4). Evidence is in agreement that morbidity due to CVD occurs at an earlier age in the SCI compared to the general population (4, 5) and we have reported that arterial stiffness may be an early sign of disease risk (4, 6).

Cardiovascular dysfunction following SCI stems in part from impaired autonomic nervous system control of hemodynamic reflexes that maintain homeostasis during the activities of daily living

(7). Sympathetic control of the upper extremity vasculature and the heart arises from T1-T5, whereas the splanchnic bed, which holds a majority of blood volume, and the lower extremity vasculature receive sympathetic input from T5-L2 (8). Parasympathetic innervation of the heart remains intact; however the synergistic function of both systems is disrupted causing segmental (lesion level) differences in sympathetic vascular control. In particular, diminished sympathetic cardiovascular control in individuals with lesions above T6 results in blood pressure (BP) instability which manifests as persistent hypotension, orthostatic hypotension and autonomic dysreflexia (8, 9). Importantly, restoration of autonomic dysfunction has been ranked as a higher in priority than regaining the ability to walk in individuals with chronic SCI (10, 11). We demonstrated that ~25% of Veterans with SCI met the World Health Organization definition of hypotension (systolic BP ≤110 mmHg in males and ≤100 mmHg in females) (13), but less than 1% were diagnosed or treated (14). Additionally, our lab has reported evidence of BP instability, defined as fluctuation in systolic BP of more than 20 mmHg above or below average BP, in persons with SCI regardless of the level of injury (12), which has been linked to impaired sympathetic nervous system function and altered plasma catecholamine responses (15) to daily shifts in orthostatic gradients (16).

A common clinical problem affecting quality of life in the SCI population is orthostatic hypotension. According to a Consensus statement from the American Autonomic Society and American Academy of Neurology, orthostatic hypotension is defined as a decrease in systolic BP of ≥ 20 mmHg and/or a fall in diastolic BP of ≥ 10 mmHg, with or without symptoms (17). The prevalence of orthostatic hypotension is increased in individuals with cervical compared to individuals with thoracic lesions, irrespective of the completeness of injury (18), and orthostatic provocations during physical therapy in newly injured patients have been shown to decrease BP in 74% of individuals with SCI, which had a negative impact in rehabilitative outcomes (19). Interestingly, decreased plasma norepinephrine (NE) has been noted in individuals with cervical lesions in the seated position when compared to individuals with thoracic injuries and uninjured controls (20, 21), and change in plasma NE in response to an orthostatic challenge was blunted in individuals with cervical lesions compared to controls (6, 22). Additionally, lower levels of NE have been found to be associated with an increased incidence of orthostatic hypotension in persons with cervical SCI (23). On the other hand, individuals with lesions below the cervical spine have normal to high levels of plasma NE concentrations (6, 20, 21) and, as a result, are less prone to hypotension and orthostatic hypotension (22). In the absence of an integral sympathetic nervous system response to orthostasis, it is postulated that individuals with cervical injury rely more heavily on the renin-angiotensin-aldosterone system (RAAS) during postural challenges (6, 12, 24, 25).

The RAAS controls long-term BP through a cascade of hormones released into the plasma in response to a drop in BP or blood volume (26), and evidence in the general population links activation of the RAAS with undesirable vascular restructuring and remodeling (27, 28). Hyperactivity of RAAS causes an increase in oxidative stress, which leads to the formation of reactive oxygen species that has been shown to affect cell signaling and induce inflammation, vascular fibrosis and calcification (27). Furthermore, angiotensin II (ANG II), a potent vasoactive peptide, acts on the endothelium, to stimulate mitochondrial protein kinase C and ATP-dependent potassium channel opening, promoting further reactive oxidative stress (29). Plasma renin was shown to increase more significantly in individuals with cervical injuries during a head-up tilt maneuver as compared to individuals with thoracic injuries and uninjured controls (23, 30). Plasma renin stimulates the release of ANG II, which increases the production of aldosterone (10), and changes in plasma renin, in most situations, correlate with changes in serum aldosterone (31). Overuse of the RAAS for maintenance of BP homeostasis during orthostatic challenges may predispose individuals with SCI to premature vascular aging as has been reported in the general population (32).

Premature vascular aging has been proposed in response to structural changes that include degeneration of elastin, increases in collagen and thickening of the arterial walls, which can be estimated non-invasively by pulse wave velocity (28). As a vessel stiffens, the velocity of blood flow increases, and the reflected pressure wave form reaches the heart during systole rather than during diastole, amplifying systolic pressure and cardiac afterload (33). A number of studies have shown that

carotid-femoral pulse wave velocity, a direct measure of arterial stiffness and the “gold-standard” , is associated with higher CVD risk (34, 35) and is recognized as an independent predictor of disease risk in the general population (36). A 1 m/s increase in pulse wave velocity corresponds to a 15% increase in total cardiovascular events and mortality in the general population (36) and an increase in pulse wave velocity of 2-3 m/s is reported in the SCI population (6, 12, 33, 37, 38-40).

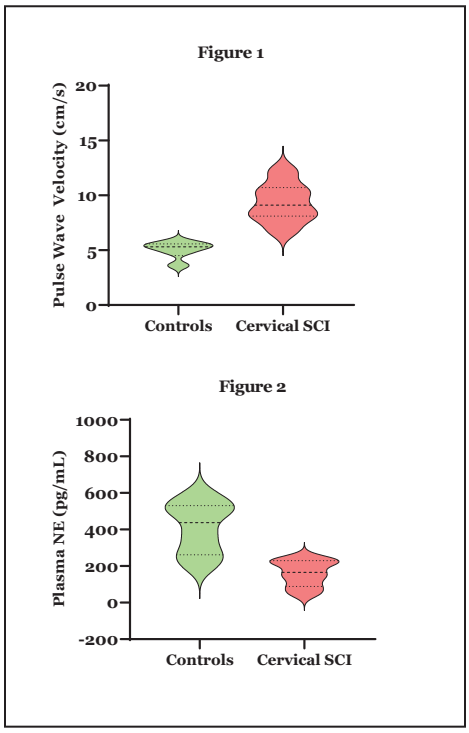
Increases in pulse wave velocity have been reported in otherwise young, healthy individuals with SCI (6, 12, 13, 19, 42-44).We reported that individuals with SCI with more severe and more frequent orthostatic hypotension are predisposed to significant increases in arterial stiffness as compared to individuals with SCI who do not experience orthostatic hypotension (4, 33). In fact, we reported an inverse relationship between seated systolic BP and arterial stiffness in individuals with SCI (4). To expand on this finding, we investigated the relationship between BP and hormonal responses to an orthostatic maneuver and demonstrated significantly lower plasma NE and significantly increased change in plasma renin during an orthostatic provocation in individuals with cervical SCI at as compared to individuals with thoracic SCI and control groups. (6). Further, we found that the relationship between pulse wave velocity and orthostatic changes in plasma renin was significant among the groups, particularly in those with cervical SCI (6). These data suggest that maintaining orthostatic BP may reduce dependency on RAAS and lower CVD risk.

Numerous experimental and clinical studies have documented reversal of detrimental vascular remodeling following RAAS blockade with either an angiotensin converting enzyme inhibitor (ACEi) or ANG II receptor blockers. In the landmark Heart Outcomes Prevention Evaluation trial – hypertensive participants randomized to the ACEi Ramipril (10mg) for 5-years had a 22% lower relative risk of cardiovascular death, stroke and myocardial infarction as compared to hypertensive participants randomized placebo (41). However, these pharmacological options are contraindicated in hypotensive individuals with cervical SCI. In fact, we demonstrated that the use of anti-hypotensive i.e., hypertensive, medications, increased mean BP and reduced active plasma renin levels and serum aldosterone during a 45° head-up tilt maneuver in individuals with cervical level injuries (42). We recently reported increased BP instability after administration of a single dose of midodrine (10mg) in hypotensive individuals with SCI (43). These data suggest that maintaining orthostatic BP may reduce dependency on RAAS and lower CVD risk, but available clinical options are limited and perhaps contraindicated for wide-spread use in the SCI population. Therefore, alternate methods of stabilizing orthostatic BP within a normotensive range should be explored for use in the SCI population.

Mounting evidence supports the targeted use of electrical stimulation of the spinal cord to modulate autonomic nervous system circuity and promote restoration of orthostatic BP control (44-47). To date, there is only one recent paper describing the effects of non-invasive transcutaneous spinal cord stimulation (TSCS) to increase BP during an orthostatic provocation. The TSCS parameters included electrode placement at the thoracic-7/8 vertebral level, using 10-70 mA current at 30 Hz, with monophasic, 1-ms pulses and the results demonstrated increases in orthostatic BP, improved cardiac contractility, and increased CBFv during active stimulation in 5 individuals with motor complete SCI (48). However, the investigators used TSCS at only one electrode placement site, and did not provide rationale for the electrode placement site, the frequency or pulse width chosen (48). The authors noted quiet electromyography (EMG) recordings of the lower-limb during stimulation, and conclude that the BP response were not attributed to the skeletal muscle pump action (48). The increase in orthostatic BP were therefore ascribed to excitation of sympathetic pre-ganglionic neurons leading to vasoconstriction and they conclude that TSCS may be a viable therapy for restoring autonomic cardiovascular control after SCI (48). However, we need to understand the effects of varied electrode placement site, and stimulation parameters (Hz, mA, pulse width) on BP and autonomic function before wide spread utility of TSCS can be recommended for clinical intervention.

Significance of the Research:

Although life expectancies have improved in the SCI population, longevity remains below the general population, due to an increased incidence of CVD, which is a leading cause of mortality in individuals with chronic SCI. Autonomic nervous system dysfunction and BP instability contribute to the increased CVD risk in the SCI population; however, because a majority of individuals with SCI remain asymptomatic the diagnosis and treatment of BP instability is not a clinical priority. This is due, in part, to the lack of safe and effective interventions, even though mounting evidence strongly supports adverse effects of BP instability on the cerebral circulation, cognitive function, and quality of life. Identifying individualized TSCS parameters that safely and effectively increase and stabilize BP in hypotensive veterans with SCI will provide the foundational evidence to support eventual wide-spread clinical utility throughout the VA healthcare system. It is anticipated that these data will begin to establish a standard methodology for TSCS mapping of spinal autonomic circuits to promote restoration of orthostatic BP, which will be used in my CDA-2 application to investigate the enduring effects of TSCS as a viable treatment option to improve participation in daily activities, independence and quality of life for veterans with SCI and other immobilizing conditions.



Preliminary Studies:

Our recent findings indicate significantly increased pulse wave velocity in hypotensive individuals with cervical SCI compared to healthy controls (9.3±1.8 versus 5.1±0.8 m/s, respectively; $p<0.0001$) (Figure 1). Although in the general population increased pulse wave velocity is associated with hypertension (52), BP was significantly lower in the individuals with SCI, due to significantly lower plasma NE concentrations compared to the controls group (Figure 2). The relationship between pulse wave velocity and orthostatic changes in plasma renin was significant, which suggests that reliance on the RAAS for BP maintenance may lead to long term vascular damage and increased CVD risk. Therefore, improving cardiovascular autonomic function and reducing reliance on the RAAS for orthostatic BP control may be expected to lower pulse wave velocity and CVD risk, thereby promoting long term health and vitality in Veterans with SCI.

Dr. Forrest within the Center for Spinal Stimulation has been investigating the effects of stimulation of the spinal cord sites on multiple integrated physiological systems, including supraspinal cardiovascular control (49-52). We investigated TSCS on BP in one individual with C5-6 AIS B SCI; electrode placement was at the C7-T1 spinous process and stimulation amplitude was ramped at 5 mA increments starting at 0 mA until a maximum intensity of 80 mA. Continuous beat-to beat BP was monitored throughout the protocol. The period of assessment included a no stimulation period (~ 1 minute), a ramp up in stimulation intensity, followed by a ramp down in amplitude and an additional

no stimulation period (~1 minute). Progressive increases in systolic BP are noted with increasing TSCS amplitude (**Figure 3**).

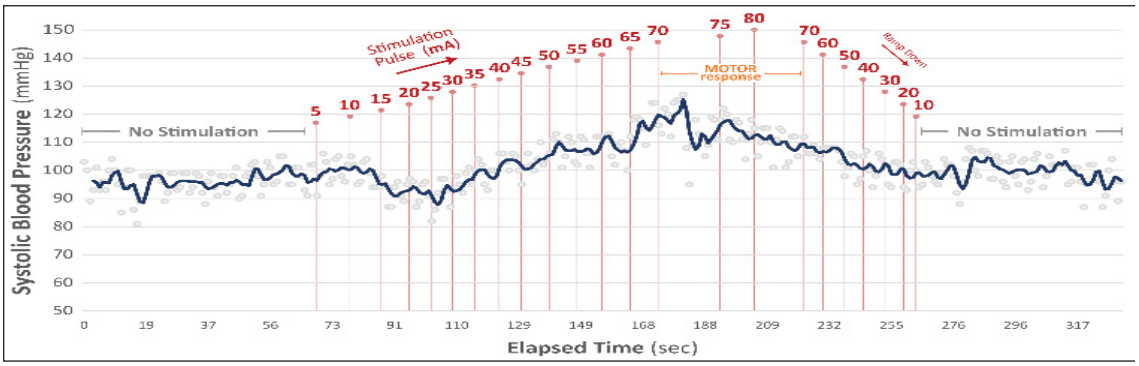


Figure 3. Blood pressure response to graded administration of TSCS in one individual with C5-6 AIS B SCI; electrode placement was at the C7-T1 spinous process and stimulation amplitude was ramped at 5 mA increments starting at 0 mA until a maximum intensity of 80 mA.

Research Design and Methods

Study Participants: It is our goal to recruit 12 eligible hypotensive individuals with injuries T6 and above. We anticipate recruitment of 4-5 eligible individuals each year of the project. Individuals with SCI will be recruited from the Northern New Jersey SCI Model System database via study solicitation flyer distribution at support groups and inpatient and outpatient treatment facilities.

Inclusion Criteria:

- Between the ages of 21-70 years old;
- Individuals with traumatic spinal cord injuries at or above T6;
- Duration of injury is more than 1 year;
- Non-ambulatory;
- American Spinal Injury Association Scale A, B or C;
- Able to provide consent;
- Non-ventilator;
- Hypotensive (Males: systolic blood pressure less than 110 mmHg and/or diastolic blood pressure less than 70 mmHg; Females: systolic blood pressure less than 100 mmHg and/or diastolic blood pressure less than 70 mmHg).
- Orthostatic hypotensive (decrease in systolic blood pressure of at least 20 mmHg and/or decrease in diastolic blood pressure of at least 10 mmHg when moving from supine to upright position) (will be determined in the screening process).

Exclusion Criteria:

- Acute illness or infection;
- Current smokers within 1 year of study;
- Documented history of controlled or uncontrolled diabetes, any other neurological condition other than a spinal cord injury (multiple sclerosis and Parkinson's disease);
- Cardiovascular disease (coronary artery disease, congestive heart failure, peripheral artery disease, stroke);
- Present or history of thrombosis in the last 12 months;
- Severe contractures.

Methods & Procedures:

We aim to compare stimulation parameters (frequency and amplitude, 1-ms pulses) using a monophasic waveform for different spinal segment sites to modulate BP. Sites for stimulation during a series of seated experiments will include 1) T 7/8; 2) T 9/10; 3) T11/12; and 4) L1/2, while beat-to-beat seated BP is continuously monitored and recorded in hypotensive individuals with SCI.

This study will take approximately 7-study visits, between 1-3 hours, per subject. Participants will be asked to arrive between 8:00 am and noon at the James J Peters VA Medical Center (JJP VAMC), after a normal breakfast and a good night sleep. The participants will be asked to not drink alcohol or caffeine 12 hours prior to their visit and there will be at least 3 days between study visits.

Approach: We will compare the electrode placement sites and amplitude during seated rest to modulate BP. We anticipate that BP responses will vary among the participants regarding the location of the electrode placement site and signal amplitude. Participants will visit the laboratory 8 times: visit 1): informed consent and medical intake to determine eligibility for enrollment in the study. Visits 2-8: amplitude (mA) mapping sessions at each electrode placement site (randomized), with continuous beat-to-beat BP monitoring at the finger arteriole and at 1-minute intervals at the brachial artery.

In-person Interview, Consent Process and Eligibility determination and Orthostatic challenge without stimulation– Visit 1**:** Paperwork including consents and medical history will be conducted by the investigator for each participant. Participant eligibility will be determined by inclusion/exclusion criteria listed in the Human Subjects documentation. Cardiovascular systemic hemodynamics (heart rate and BP) will be measured in the seated position for 5 minutes. The participant will then lie down in the supine position for 10 minutes prior to collecting pulse wave velocity at the carotid and femoral artery. A blood sample of renin, aldosterone and NE will be drawn and continuous beat-to-beat heart rate, BP and CBFv will be recorded for 5 minutes. Participants will then we secured to a tilt table and will be tilted to 30°, 45° and 60° for 10 minutes at each angle with continuous beat-to-beat monitoring of the systemic hemodynamics. A second blood draw of renin, aldosterone and NE will be drawn at the end of 10 minutes at 60° tilt (**Table 2**). Participants will be deemed eligible for the TSCS mapping if their BP response to the head-up tilt maneuver meets the definition of orthostatic hypotension. A six-item validated orthostatic hypotension questionnaire will be used during the orthostatic tilt visits to report associated symptoms (54) (**Appendix**). Participants will undergo response to stimulation prior to entry to study and will be monitored for suitability to study protocol by Dr. Forrest prior to stimulation.

Amplitude Parameter Mapping Visits 2-8: Before TSCS, electrodes will be placed on the vertebral midline at the spinous process (T7/8, T9/10, T11/12, L1/2), and the active site will be randomized. Each visit, we will complete one electrode placement site. Amplitude ramping will start at 10mA, with 10mA increments (pulse width, 1ms, frequency 30 Hz as shown (13)). Continuous real-time BP and heart rate will be measured for 5-minutes, before, during and after stimulation. During ramping, amplitude will stop increasing when SBP reaches optimal SBP between 110-120 mmHg (100-120 mmHg females) or reaches 100 mA with no SBP response (see below TSCS decision Tree). Amplitude will be decreased in 10 mA decrements in stimulation. BP will be continuously recorded during the rest period. Bilateral muscle activation (rectus femoris, medial hamstring, and gastrocnemius) will be monitored during all experiments to determine if skeletal muscle contractions are contributing to increases in BP. Additionally, signs and symptoms of autonomic dysreflexia will be monitored during TSCS testing in visits 3-6 by a questionnaire (**Appendix**). After every incremental increase of amplitude, investigator will ask participant if he/she is experiencing any symptoms. Maximum ramping amplitude will be 100 mA and testing will be halted if participant experiences any discomfort during testing. Based on preliminary work, regulation of neuromodulation of BP will occur at stimulation levels less than 100mA.

Participants will be notified by investigator is any of the findings from this study will affect the participants' health or welfare.

- Cardiovascular Assessments: While the subject is seated 3 ECG electrodes will be affixed to the chest and abdomen for continuous monitoring of HR and respiration rate (RR). Brachial BP will be monitored at 1 minute intervals using a standard adult BP cuff placed at the right upper arm, and beat-to-beat finger arteriolar BP will be continuously monitored from the right

middle finger throughout testing. Mean arterial pressure (mmHg) will be calculated from brachial BP using the formula: [systolic BP + (2* diastolic BP)]/3. Beat-to-beat HR, RR and BP data will be viewed in real-time and stored for subsequent analysis using customized programs created with LabView graphical software.

- Transcutaneous spinal cord stimulation: Digitimer DS7A will be used to provide constant current voltage of electrical activity during the mapping and final orthostatic challenge. TSCS electrodes at different sites on the spinal process (T7/8, T9/10, T11/12, L1/2) and various amplitudes and frequencies will be assessed to determine the optimal site to increase blood pressure and decrease symptoms of orthostatic hypotension.

TSCS Blood Pressure (BP) decision tree

Intensity ramp starting at 10 mA and increasing at 10 mA intervals until:

1. **Intolerable to patient**
    a. If uncomfortable, but tolerable, lower increments to 5mA increase/interval

2. **Sustained BP response - 3 or more manual systolic BP within the target range:**
   MALES: systolic BP 110-120 mmHg; FEMALES: systolic BP 100-120 mmHg

    a. At each mA interval a manual blood pressure is taken ~1 minute:
        i. **IF:** systolic BP increases by 10 mmHg above baseline repeat BP recording
        ii. **IF:** still 10 mmHg above baseline take a third BP recording.
        iii. **IF:** still 10 mmHg - but < 100 mmHg (< 90 females mmHg) increase by 10 mA and repeat manual BP assessments.
        iv. **IF:** still 10 mmHg - but < 110 mmHg (< 100 mmHg females) increase by 5 mA and repeat manual BP assessment.
        v. **IF:** between 110-120 mmHg (100-120 mmHg females) stop intensity ramp and monitor BP for 10 minutes at that mA ramp.
        vi. **IF:** only 1 or 2 readings that are 10 mmHg above baseline continue incremental ramp at 10 mA.
        vii. **IF:** during the 10-minute assessment systolic BP drifts down to < 110 but > 100, continue ramp at 5 mA.
        viii. **IF:** during the 10-minute assessment systolic BP drifts down to < 100, continueramp at 10 mA.

3. **Reach a stimulation intensity of 100 mA without a blood pressure response or intolerable symptoms.**

Risk and Discomforts:

- Heart Rate, Arterial Stiffness and Blood Pressure: These are non-invasive procedures that involve minimal risk; however, some participants may experience discomfort when the ECG electrodes are removed from the skin and when the blood pressure cuffs are inflated.
- Transcutaneous stimulation: Participants may get headaches, autonomic dysreflexia, skin breakdown at the electrode placement site, pain, severe contractures (fractures) and muscle tears. If any of these potential risks occur, the stimulation will cease immediately and the investigators will monitor the situation.

As with any research, there may be unforeseen risks and discomforts. Dr. Noam Y. Harel, a medical doctor associated with the study, will be available and present during testing to for clinical intervention if necessary or to treat any medical emergency.

Study Compensation:

Participants will be given a study compensation of $100 for each study visit (9 total visits); participants could earn a total of $900 for completing all study visits.

Costs:

This protocol has been funded by VA Research and Rehabilitation and all costs associated will be covered by this grant.

Publication of Research:

It is anticipated that the observations made in this study will be presented at National and International meetings and will be submitted for publication in peer-reviewed journals, including those in the fields of Spinal Cord Medicine and neurology.

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