Thermoregulation and Cognition During Cool Ambient Exposure in Tetraplegia

NCT02379156

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RESEARCH PROTOCOL

1. SPECIFIC AIMS.

Problem Statement: After a cervical spinal cord injury (SCI) the motor, sensory and autonomic deficits cause, among other detriments, a blunted ability to maintain a constant core body temperature (Tcore). Impaired thermoregulation leaves persons with tetraplegia more susceptible to hypothermia than able-bodied persons (AB). In addition, the commonly prescribed medications to treat the spasticity, pain, and depression that accompany this injury, raise the vulnerability of this population to hypothermia, and its potentially fatal consequences.

Persons with tetraplegia are routinely exposed to cool ambient temperatures in their homes, work environments, and while waiting on or riding in accessible public transportation. The thermoregulatory response and cognitive consequences of prolonged exposure to cool temperatures have not been investigated in persons with tetraplegia. Preliminary data has suggested that even limited exposure to cool temperatures can cause a drift in Tcore to values approaching hypothermia. With this lowering of Tcore, cognitive performance may also be negatively affected. Such demonstration of mild (or worse) hypothermia and concomitant declines in cognitive function would warrant investigations of interventions to mitigate this drift in persons with tetraplegia. The International Spinal Cord Injury Skin and Thermoregulation Basic Data Set is further evidence of the growing recognition that many people with SCI are affected by thermoregulatory dysfunction.

There has been a paucity of work addressing the thermoregulatory responses of persons with SCI to cool ambient temperatures, and even less study of medical interventions to improve maintenance of Tcore. Although it is presently unknown as to whether a modest fall in Tcore impairs cognition in persons with SCI, one may expect deterioration in cognitive function because central neurological function is exquisitely temperature sensitive. As such, cognitive performance will be determined after decrement in core body temperature.

The goals of this study are: 1) to improve our understanding of the thermoregulatory mechanisms of individuals with tetraplegia when exposed to cold, 2) to determine if cognitive performance is affected after a decrement in Tcore, and 3) to determine if administration of an alpha-adrenergic agonist (midodrine) delays or decreases the expected downward drift in Tcore and possible deterioration of cognitive performance.

In order to address our goals, we have designed a study methodology which consists of comparing the physiological and subjective responses of the two study groups (tetraplegia versus AB controls) from thermoneutral (27°C) to cool (18°C) environments in the seated position. On a 2nd visit, the subjects with tetraplegia who completed the first visit, will be given midodrine while seated prior to being placed in the cool environment to compare their responses with midodrine to their responses to the identical challenge without midodrine.

Overall Objective: The overall objective is to identify and address the physiological and cognitive problems that persons with spinal cord injury (SCI) face when exposed to routinely encountered cool temperatures.

- **Specific Aims:** during exposure to a cool environment (18°C) for up to 120 min in the seated position:

Primary Specific Aim: To determine the change in: (1) Tcore and to assess (2) cognitive performance (attention, processing speed, working memory, and executive function) before and

after exposure to cool temperatures. **Primary Hypotheses:** Based on our pilot data: (1) Sixty-six percent of persons with tetraplegia and none of the controls will demonstrate a decline of 1.0°C in Tcore; (2) Eighty percent of persons with tetraplegia and 30% of controls will have a decline of at least one T-score in Stroop Interference scores (a measure of executive function).
Secondary Specific Aims: To determine the change in: (1) the average of distal skin temperatures, (2) metabolic rate, and (3) subjective rating of thermal sensitivity. **Secondary Hypotheses:** Persons with tetraplegia will have less of a percent change in average distal skin temperatures and metabolic rate, and report blunted thermal sensitivity ratings compared with able-bodied (AB) controls.
Tertiary Specific Aim: To determine if a 10 mg dose of midodrine will (1) reduce the decrease in Tcore and (2) prevent or delay the decline in cognitive performance in the group with tetraplegia.
Tertiary Hypothesis: Because the one-time, off-label use of midodrine will address the primary systemic impairment to cold exposure in persons with tetraplegia, lack of peripheral vasoconstriction, the induced vasoconstriction will serve to reduce cutaneous heat losses and will be anticipated to blunt the decrease in Tcore and delay the decline in cognitive performance compared to cool exposure without drug administration.

METHODS

Research Design and Methods: A prospective, two-group comparative study will be performed to determine the effects of cold thermal challenge on Tcore, cognitive performance, distal skin temperatures (Tsk), metabolic rate (VO_2), and thermal sensitivity (TS) in the seated position in individuals with tetraplegia and in a matched AB control group (Visit 1). During Visit 2, a prospective, within-group comparative study will be performed to determine the effects of cold thermal challenge on Tcore, cognitive performance, Tsk, VO_2, and TS only in individuals with tetraplegia after midodrine administration compared to their response on Visit 1.

A prospective, two-group comparative study will be performed to determine the effects of cold thermal challenges on core temperature measured by rectal thermocouple (Tre), skin temperature by surface thermocouples (Tsk), cognitive performance by [digit span section of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV), Stroop Color and Word tests, Symbol Digit Modalities Test (SDMT), memory and delayed recall sections of the Montreal Cognitive Assessment (MoCA)], metabolic rate measured by oxygen consumption (VO_2), and thermal sensation by the thermosensitivity cold scale in the seated position in individuals with tetraplegia and in a matched AB control group (Visit 1). During Visit 2 a prospective, within-group comparative study will be performed to determine the effects of thermal challenge on Tcore, skin temperature, cognitive performance, metabolic rate, and thermal sensation in individuals with tetraplegia who have participated in Visit 1 and in those same individuals who repeat the Visit 1 challenge identically, except for the administration of midodrine prior to the cold challenge while in the seated position (Visit 2).
Subjects: Fifteen subjects with tetraplegia (C4-T1) and 15 non-SCI control subjects matched for age (± 5 years), and gender will be recruited for study.

Subject Recruitment:
Patients referred by their physician following routine physical examinations will be approached for possible study enrollment. Physicians will be informed of the inclusion and exclusion criteria for this study and will be able to provide us with the assurance that the patient is an appropriate study subject and that they were willing to speak with the study coordinators.
Veterans with SCI responding to IRB approved articles in lay publications and advertisements.
Veterans with an ongoing relationship with our center, such as through attendance at one of the following SCI clinics: (1) Metabolic, (2) Pulmonary, or (3) GI.

a. Inclusion criteria
    1. Between 18 and 68 years of age;
    2. Duration of injury ≥ 1 year;
    3. Level of SCI C4-T1; (AIS A & B)
    4. Euhydration (Subjects will be instructed to avoid caffeine and alcohol, maintain normal salt and water intake, and avoid strenuous exercise for 24 hours prior to study); and
    5. Age (± 5 years) and gender matched AB control group.
b. Exclusion criteria
    1. Evidence of sympathetic integrity below the lesion level by the skin axon-reflex vasodilatation (SkARV) test (a distinctly diminished vasodilatory response to mechanical stimulation of the skin is evident below the lesion level when sympathetic integrity has been interrupted);
    2. Known allergies to midodrine hydrochloride;

    Exclusion Criteria shared by subjects with SCI and AB controls

    3. PMH of diagnosed heart, kidney, peripheral vascular, or cerebral vascular disease, or diabetes mellitus;
    4. Hypertension (BP>140/90 mmHg);
    5. Untreated thyroid disease;
    6. Acute illness or infection;
    7. Current smoker;
    8. Pregnancy.

Preparation for Study Visits: AB controls will be gender- and age-matched (±5 years) to subjects with SCI. All subjects will be instructed to avoid caffeine and alcohol, maintain normal salt and water intake, and avoid strenuous exercise for 24 hours prior to study to ensure euhydration. Subjects will enter the laboratory between 8:00-10:00 AM on each study visit. Study visits will be separated by a minimum of 1 day and no more than 14 days. Subjects will wear minimal clothing (gym shorts, sports bra) during the study to maximize skin exposure to the cool temperature. Each subject will be asked to eat a light, standard meal (plain bagel or 2 pieces of toast) 2 hours prior to their visit. Subjects will be asked to empty their bladders prior to each study visit and again upon arrival, if needed.

Visit 1: Cool Ambient Challenge: Instrumentation: During Visit 1, all subjects will be instrumented on a padded table, after which they will be transferred back to their wheelchair or, for controls, to a provided wheelchair. All subjects will use a Roho seat cushion (high-profile single compartment ROHO seat cushion, the Roho Group, Belleville, IL) for air circulation consistency and decubiti prevention. A rectal probe will be placed 10 cm beyond the anal sphincter for core temperature collection, and skin thermocouples will be secured at 15 sites above and below the level of lesion for collection of skin temperatures. A dilution mask will be placed over the subject's nose and mouth for collection of exhaled gases from which resting metabolic rate will be calculated from analysis of expired gases (VO_2) by a metabolic cart. Laser Doppler flowmetry (LDF) will be used to measure changes in microvascular perfusion by placing a doppler probe on the skin in the area of the ulnar styloid processes and medial malleoli bilaterally (wrists and ankles) to confirm vasoconstriction. A pulse oximeter will be placed on the second digit to obtain blood oxygen saturation and heart rate (HR). A BP cuff will be placed above the right elbow to measure brachial BP. An intravenous catheter will be placed in an upper extremity vein for sequential blood draws to assess plasma NE and cortisol levels.

Baseline Collection: At the end of the 30-minute acclimation period (27°C), a baseline (BL) collection of the following parameters will be performed for 15 minutes with Tcore, Tsk, and VO_2 measured continuously; HR, BP, blood oxygen saturation, subjective measures of TS, and 5 minutes of LDF will be measured at 10-minute intervals. A venous blood draw will be collected once at baseline for NE and cortisol concentrations. At the end of the BL period, hypertonicity (spasticity) will be measured only in subjects with tetraplegia in both upper extremities, at the elbows and wrists (flexors and extensors) and both lower extremities, at the knees and ankles (flexors and extensors) using the Modified Ashworth Scale. Once the spasticity measurement is completed, a cognitive performance battery will be administered.

Thermal Challenge: Following completion of the BL period, subjects will be wheeled into an 18°C thermal chamber for 120 minutes or until Tcore ≤ 35°C. Tcore, Tsk, and VO_2 will be continuously monitored to ensure subject safety throughout the protocol; brachial BP, HR, blood oxygen saturation, TS, and symptoms of autonomic dysreflexia and hypothermia will be assessed at 10-minute intervals while LDF will be measured for 5 minutes every 20 minutes. Venous blood will be collected at 50-minute intervals. After 1 hour of Cold Challenge, hypertonicity (spasticity) will be measured again only in subjects with tetraplegia in both upper extremities, at the elbows and wrists (flexors and extensors) and both lower extremities, at the knees and ankles (flexors and extensors) using the Modified Ashworth Scale. A decrease in Tcore to ≤ 35°C, or subject discomfort, will result in termination of the protocol. The cognitive performance battery will be administered when Tcore has declined 1°C or is ≤ 35.5°C (in subjects with tetraplegia) or after 120 minutes of cold exposure (in both groups) on Visits 1 & 2.

Visit 2: Cold Ambient Challenge with Midodrine: Visit 2 will be completed in subjects with tetraplegia who participated in Visit 1 and who had an impaired ability to maintain Tcore. Following completion of the BL period, hypertonicity (spasticity) will be measured only in subjects with tetraplegia in both upper extremities, at the elbows and wrists (flexors and extensors) and both lower extremities, at the knees and ankles (flexors and extensors) using the Modified Ashworth Scale. Subjects will then be orally administered midodrine hydrochloride (10 mg). Forty minutes after midodrine administration (for onset of drug effect), a second BL collection will be obtained, and hypertonicity (spasticity) will again be measured only in subjects with tetraplegia in both upper and lower extremities. Subjects will then be wheeled into the 18°C thermal chamber for 120 minutes or until Tcore ≤ 35° C. Data collection will follow the same schedule and be conducted in the seated position as in Visit 1. After 1 hour of Cold Challenge, hypertonicity (spasticity) will again be measured in both upper and lower extremities.

Statistical Analyses: *Visit 1:* Depending on the data distribution, parametric or non-parametric analyses will be performed. For the within-group comparisons, paired-t and Wilcoxon signed rank tests will be conducted to determine intra-group differences in the dependent variables. For the between-group comparisons, unpaired-t and Mann-Whitney U tests will be performed to determine between-group differences in the percentage change (from thermoneutral to cool) of the dependent variables (Tcore, cognitive performance, Tsk, and VO_2).
Visit 2 (with midodrine): Depending on the data distribution, parametric or non-parametric analyses will be performed. Within the group with tetraplegia, paired-t or Wilcoxon signed rank tests will be used to determine differences in the percentage change (from thermoneutral to cool) of the dependent variables (Tcore, cognitive performance, Tsk, VO_2), without midodrine (Visit 1) compared to with midodrine (Visit 2).

Sample size: The primary outcome variables are Tcore and cognitive performance. For Tcore, using our preliminary data obtained post cold exposure in tetraplegic and AB subjects, mean Tcores of 35.95±0.63°C and 37.3±0.28°C were demonstrated, respectively. The difference between the groups for these values yields a power of 99.9% at an alpha of 0.05 with 8 subjects

per group (double-sided). Four of the 6 subjects with tetraplegia (66%) had a decrease of ≥ 1.0°C while no control demonstrated a decline > 0.297°C in Tcore (0%). Cognitive performance will be assessed after a Tcore decline of 1.0°C in subjects with tetraplegia. Using 66% (tetraplegia) versus 0% (control) with a count of 15 per group, the power is 99.59% at an alpha of 0.05. We are hypothesizing that 66% of subjects in the SCI group will have a decline of 1.0°C in Tcore while none of the controls will demonstrate the same decline. We are well-powered to test this endpoint. For cognitive performance, preliminary data indicated that 5 of 6 subjects with tetraplegia (83%), compared to 2 of 6 AB subjects (33%), demonstrated a decline of ≥ 1 T-score in Stroop Interference scores post cold exposure. Using 83% (tetraplegia) versus 33% (control) with a count of 15 per group, the power is 82.75% at an alpha of 0.05 (double-sided).[76] We hypothesize that 80% of subjects in the SCI group will have a decline of at least 1 T-score in Stroop Interference scores while 30% of controls will demonstrate that same decline. We are well-powered to test this outcome.