D1734-P

Effect of Heat Exposure on Cognition in Persons With Higher Cord Lesions

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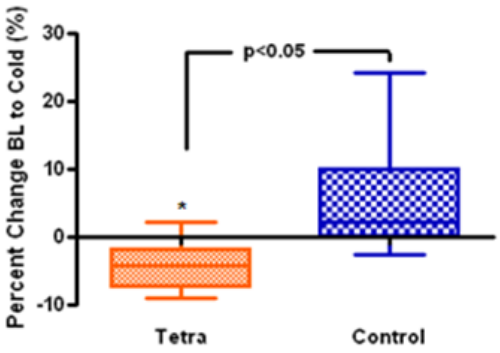
The increased variability in Tcore of persons with SCI has been demonstrated in a previous study. Nine subjects with tetraplegia and 8 matched controls ingested a capsule which transmitted information on temperature to a portable receiver (manuscript in preparation). Subjects were sent home to perform their usual routines (i.e., their activities and environments were not controlled). Tcore was measured 3 times when the capsule was in the small intestine. The variance in the mean of these 3 measurements was more than 200% greater in those with tetraplegia than in controls (0.71±0.06 versus 0.31±0.04; respectively, $p<0.01$).

Fig 3: Percentage Change of Stroop Interference Scores from BL to Cool challenge



Legend: Percentage change of Stroop Interference Scores from 27°C (BL) to after18°C ambient temperature challenge (Cool).

Research Design and Methods

Research Design: Methods: A prospective, two-group comparative study will be performed to determine the effects of warm thermal challenge on Tcore, cognitive performance, distal skin temperature (Tsk), sweat rate (QS), and subjective rating of thermal sensitivity (TS) in individuals with SCI (tetraplegia and high paraplegia) and in a matched AB control group in the seated position.

Subjects: Twenty subjects with higher cord lesions (C3-T4; AIS A & B) and 20 non-SCI controls, 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 and will be able to assure us that the patient is an appropriate study participant and that he/she is willing to speak with the study coordinators.

1. Veterans with SCI responding to IRB approved articles in lay publications and advertisements.
2. Veterans with an ongoing relationship with our center (Metabolic, Pulmonary, or GI SCI clinics).
   a. Inclusion Criteria: (1) Between 18 and 65 years of age; (2) Duration of injury ≥1 year; (2) Level of SCI C3-T4, AIS A & B; (3) Tcore at BL <37.0°C; (4) Euhydration; and (5) Gender and age-matched (±5 years) AB controls (between 18-65 years of age).
   b. Exclusion Criteria: (1) Known heart, kidney, peripheral vascular or cerebral vascular disease; (2) High blood pressure; (3) History of TBI or diagnosed cognitive impairment; (4) Untreated thyroid disease; (5) Diabetes mellitus; (6) Acute illness or infection; (7) Dehydration; (8) Smoking; (9) Pregnancy; and (10) Broken, inflamed, or otherwise fragile skin.

Preparation for Study Visits: 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**]** will enter the laboratory between 8:00-10:00 AM on each study visit. Subjects will wear minimal clothing during the study to maximize skin exposure to the warm 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.

Warm Ambient Exposure: Instrumentation: Subjects with SCI will be asked to remain in their wheelchairs and AB controls will be placed in a manual wheelchair, where they will **[**remain seated and relatively still**]** for the duration of the study visit. A rectal probe will be placed 10 cm beyond the anal sphincter for Tcore collection, and skin thermocouples will be secured at 15 sites above and below the level of lesion (e.g., bilateral toes, feet, thighs, upper and lower chest, triceps, hands, fingers, and forehead) for collection of skin temperature. Sweat collection capsules will be placed on the left lateral anterior shoulder, volar aspect of the distal forearm, proximal anterior thigh and the mid-lateral calf (dermatomes C5, T1, L3, L5) for measurement of sweat rate by QSweat methodology (QS). Laser Doppler flowmetry will be used to measure changes in microvascular perfusion (MVP) by placing a Doppler probe on the dorsal surface of both hands and feet to confirm peripheral vasodilatation. An automated blood pressure cuff will be placed above the left elbow to measure brachial BP.

Baseline Collection (BL): At the end of the 30 minute acclimation period at 27°C, a baseline collection of the following parameters will be done in the following order for 15 minutes: Tcore and Tsk, QS, MVP along with BP and HR. Subjective measures of thermal sensation and discomfort will be obtained using a 9-point thermal sensation scale (TS). After 15 minutes, a battery of cognitive tests will be administered to establish baseline cognitive performance (attention, working memory, processing speed, and executive function).[69-73]

Thermal Challenge (Heat): Following completion of BL, subjects will be wheeled into a pre-heated (35°C) thermal chamber for up to 120 minutes or until Tcore increases 0.5°C. Tcore and Tsk will be continuously monitored to ensure subject safety throughout the protocol while HR, BP and TS will be assessed at 10 min

intervals. MVP and QS will be measured every 30 minutes. The same battery of cognitive tests will be administered when Tcore increases 0.5°C from BL values (for subjects with tetraplegia) or after 100 minutes of Heat (for controls) to determine any change in cognition after exposure to 35°C. An increase in Tcore ≥0.5° C, significant changes in BP or subject discomfort will result in termination of the protocol.

Dr. William Bauman will be the physician directly responsible for subjects' medical safety during the study protocol. We have the equipment, ability, and expertise to monitor the subject's Tcore, heart rate and BP, at regular and frequent intervals. Symptoms suggestive of hypotension, autonomic dysreflexia, or hyperthermia will also be assessed every 10 minutes. Dr. Bauman will be notified immediately of any symptoms or signs of concern; he will assess the subject promptly and will terminate the study if any safety issues should arise. If Tcore ≥ 0.5°C or after 120 min of thermal challenge is completed, the subject will be transferred to a cool room (21°C), covered with cool, moist blankets, and provided with cold fluids. If symptoms persist, Dr. Bauman will assess the subject and provide the appropriate care. Subjects will be monitored for a minimum of 30 minutes of recovery to ensure Tcore returns to within 1% of BL.

Procedures

Thermoregulatory Measurement Procedures: The following measurements will be obtained during BL, Thermal Challenge & Recovery periods. *Tcore:* will be monitored by a TX-2 Rectal probe and Iso-Thermex Multichannel Thermometer (Columbus Instruments, Columbus, OH). The probe will be placed 10 cm beyond the anal sphincter. *Skin Temperature (Tsk):* will be monitored using TX-4 Skin Surface probes and Iso-Thermex Multichannel Thermometer (Columbus Instruments, Columbus, OH). Skin thermocouples will be taped to 15 sites above and below the SCI level. *Sweat Rate (QS):* will be measured using Q-Sweat (Quantitative Sweat Measurement System, WR Medical Electronics Co., Minnesota) and 4 sweat collection capsules. *Microvascular Perfusion (MVP):* will be measured using laser probes on the skin of the dorsum of both hands and feet and a Periflux System 5000 Laser Doppler (Perimed, Stockholm, Sweden). *Thermal Sensitivity (TS)*: will be measured by a 9-point thermal sensation scale. (Appendix 3)

Table 1: Schedule of Assessments and Procedures

Measures	Acclimation	BL	Heat	Recovery
Run Time (min)	30	15	120†	30
Cumulative Time (min)	30	45	165	195
TCore		††	††	††
Skin Temperatures		††	††	††
Brachial BP		2x	12x	3x
Sweat rate (QS)		1x	3x	
Thermosensitivity Scale	1x	2x	12x	2x
Microvascular Perfusion		2x	3x	
Cognitive Battery		1X	1X	

† Heat will continue until Tcore increases 0.5°C, or until 120 minutes. †† Tcore and skin temperature measurements will be monitored and collected continuously throughout the study.

Cognitive Performance Battery: The cognitive battery will be administered once at BL and once after Tcore has increased 0.5°C after thermal challenge (in tetraplegics) or after 100 minutes of Heat (in controls). **[**Testing conditions will be identical, quiet and distraction-free.**]** *Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV):* Subjects will be asked to repeat 2-9 numbers forward, backward or in ascending order to assess attention, processing speed, and working memory. [70-72] *Memory section (Delayed Recall) of the Montreal Cognitive Assessment (MoCA):* Subjects will be asked to repeat 5 simple words immediately and then recall them after a 5 minute delay to assess working memory. [69] *Stroop Color and Word:* Subjects will be asked to read words of colors, colors of fonts to assess attention and processing speed; color of fonts of words which describe conflicting colors to assess response inhibition (executive functioning). [73] **[**Subjects will practice each of the assessments for approximately 10 seconds prior to the actual test to insure understanding of the instructions.**]**

Hemodynamic Measurement Procedures: *Brachial Blood Pressure:* will be measured at the right brachial artery using the Carescape Dinamap V100 Automated BP Monitor (Carescape, Milwaukee, WI). BP will be obtained at 10 minute-intervals throughout BL, Thermal Challenge, and Recovery periods.

Sample Size and Statistical approach: Based on power analysis from our preliminary data in 8 subjects with tetraplegia, we determined that a sample size of 20 subjects per group would be needed to achieve a power of 97.34% for a double-sided 2 sample analysis at an alpha of 0.05. If 5 subjects per group are lost to attrition, the power would be 91.66%. The primary aims that 80% of the subjects with SCI will demonstrate an increase of 0.5°C in Tcore and an increase of at least one T-score in Stroop Interference (executive function) will be analyzed using one-sample chi square tests. Secondary physiological and cognitive variables will be compared between groups using multivariate analyses (MANOVA). Significant group main effects from the MANOVA model will be further analyzed using unpaired t-tests. Percent changes from BL will be calculated for all variables and analyzed for significance against zero (i.e., no change) using one-sample tests.