Developing a Feedback-Controlled Heated Vest to Address Thermoregulatory Dysfunction in Persons with Spinal Cord Injury

NCT03662308

August 25, 2023

PART II

RESEARCH PROPOSAL

1. SPECIFIC AIMS.

Problem Statement: Loss of supraspinal control of autonomic pathways interrupts homeostasis of multiple organ systems including thermoregulation. Thermoregulatory mechanisms are dysfunctional due to interrupted sympathetic pathways for hypothalamic control of vasomotor and sudomotor function and motor/sensory pathways for shivering and thermal sensation. During exposure to warm seasonal temperatures, dysregulation of heat dissipating mechanisms (vasodilation and sweating) allows core body temperature (Tcore) to rise in persons with SCI rather than remaining stable and tightly regulated (~37±0.6°C), as occurs in able-bodied (AB) persons. We have reported in persons with higher lesions (SCI >T6: Hi-SCI), that even limited exposure (1-2 hours) to typical summer temperatures (35°C) can result in Tcore rising to values approaching hyperthermia (≥38°C). Mild hyperthermia causes physical discomfort and can impair cognition. Unchecked, hyperthermia can progress to heat exhaustion and heat stroke causing seizures, loss of consciousness, and potentially death, as occurred in vulnerable residents of the Pacific Northwest during a heat wave in late June 2021.

Current medical advice for those with SCI is to avoid direct sunlight, dress sparingly, drink plenty of fluids, and stay indoors on hot, humid days. Despite heeding this advice, persons with SCI frequently find themselves in hot environments for prolonged periods during social, religious, or work functions. During these conditions, there is rapid progression to feeling “overheated” and an increased risk for heat-related illness. Warm seasonal temperatures limit perceived comfort, performance of activities, and participation in societal functions to a greater extent in persons with cervical injury (tetraplegia) than in AB controls. Identifying a safe, non-invasive, efficacious bioengineering intervention to restore thermoregulatory function during heat exposure has the potential to minimize the negative impact of heat on activities, participation, and quality of life (QOL) in Veterans with SCI. If efficacious, other Veteran populations adversely affected by heat exposure may also benefit from this intervention.

Goals: This pilot study will develop and test a self-regulating cooling vest for Veterans with SCI that can utilize both conductive and evaporative methods to dissipate body heat as a proof-of-concept to prevent an excessive rise in Tcore and thermal discomfort during controlled exposure to a warm environment. An initial prototype of the vest has already been developed in collaboration with Dr. Hao Su, a bioengineer. A service contract has been established with Picasso Intelligence L.L.C. to further develop our initial prototype, under the leadership of Dr. Hao Su, prior to human subject testing. If this study is successful, we will collaborate with the Human Engineering Research Laboratory to make the vest appropriate for home testing to determine its effectiveness in improving societal participation and QOL in Veterans with SCI during warmer seasons or when residing in or traveling to hot climate zones. If effective, we are confident that HERL, with the assist of the VA’s Technology Transfer Program, can bring this intervention to the commercial market.

Primary Objective (Safety): To complete development of the 2nd prototype of the cooling vest and determine its safety. After satisfying bench testing criteria, AB participants will wear the wet cooling vest at maximal settings for 2 hours in the seated position in a warm thermal chamber (35°C), to determine: (1) minimum skin temperatures beneath the cooling vest and (2) subjective comfort of the cooling vest.

Primary Hypotheses: (1) Skin temperatures beneath the vest will be ≥20°C to protect against cold injury. (2) AB participants will report a thermal sensation (TS) no less than “cool” on a validated 9-point thermal sensation scale. If during testing, a skin temperature of <20°C is measured or a TS < “cool”, or “cold spots” are reported, vest development will continue to ensure that the prototype is safe for testing in persons with SCI. Once safety criteria for the cooling vest are met in AB subjects, efficacy testing will be performed in persons with SCI who will wear the cooling vest during a controlled warm challenge.

Secondary Objective (Efficacy in SCI): To determine the efficacy of the wet cooling vest to maintain Tcore (within 0.3°C) in participants with Hi-SCI when exposed to 2 hours of a warm environment. Using a repeated measures design, participants with Hi-SCI will wear the wet vest (experimental condition) or no vest (control condition) in a warm thermal chamber (35°C) for up to 2 hours in the seated position, to determine: (1) change in Tcore and (2) perception of heat and thermal comfort.

Secondary Hypotheses: In our previous investigation of heat exposure, 65% of persons with Hi-SCI had increases of >0.5°C in Tcore (mean increase 0.6±0.3°C) while wearing only shorts. We expect that

wearing a cooling vest during the same heat exposure, will significantly increase heat dissipation and, thus, enhance maintenance of Tcore and thermal comfort. We hypothesize that during a controlled warm exposure (35°C), participants with Hi-SCI wearing the wet cooling vest compared to the same participants not wearing a vest: 1) 65% will have a significantly reduced elevation in Tcore (≤0.3°C), and 2) a greater percentage of participants will report increased thermal comfort (decreased perception of feeling “hot”, “very hot”, or “uncomfortable”).

2. BRIEF REVIEW OF RESULTS OF OTHERS AND CURRENT STATE OF KNOWLEDGE

Background

The interruption of autonomic pathways after spinal cord injury (SCI) causes dysregulation of multiple organ systems, including thermoregulation.[1-4] The consequences of an impaired ability to maintain core body temperature (Tcore) may be more subtle than the limitations in activities and mobility caused by muscle paralysis due to interrupted motor pathways. Thermodysregulation negatively impacts health, personal comfort, and the willingness to participate in functions outside the home.[5,6] The prevalence of thermodysregulation in persons with SCI has not been reported, but it is related to the integrity of sympathetic pathways for vasomotor and sudomotor function and motor/sensory neurological level of injury (NLI) for shivering and sensation.[3,7] The ability to redistribute blood between central and peripheral compartments is impaired the most in persons with tetraplegia (NLI ≥ C8) and high paraplegia (NLI ≥T6) due to dysfunctional vasomotor control of central (splanchnic) and peripheral (lower extremity) vascular beds, resulting in orthostatic hypotension, as well as autonomic dysreflexia due to vascular dysregulation.[8-10]

Thermoregulation in Warm Conditions in Able-Bodied (AB) Persons

Thermoregulation is a precisely controlled homeostatic function, which maintains Tcore within a narrow range (37.0±0.6°C) despite a wide range of environmental temperature challenges.[11-14] Effective thermoregulation depends on the integrity of afferent thermal sensory information, from cutaneous and deep thermal receptors, for cortical awareness and initiation of biobehavioral responses (i.e., add or remove clothing) and for preoptic hypothalamic processing for appropriate modulation of efferent thermoregulatory responses.[15-17] Upon recognition of excessive heat storage, from either warm ambient conditions or physical activity, the hypothalamus rapidly orchestrates sympathetic-mediated responses of vasodilation and sweating to dissipate heat to maintain Tcore within the range of normothermia as well as perceived thermal comfort.[16,18,19]

Thermoregulation in Warm Conditions after SCI

In persons with SCI, the interruption of sympathetic pathways limits central regulation of vasodilation and sweating for increasing heat loss[20,21] and vasoconstriction for decreasing heat loss.[2,22] Motor pathway interruption, identified by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI),[23,24] limits involuntary shivering for thermogenesis, as well as the ability to move to more temperate environments. Interruption of sensory pathways, also identified by the ISNCSCI, impairs awareness of warm or cool ambient conditions, delaying biobehavioral responses (i.e., adding or removing clothing) and the ability of the hypothalamus to rapidly orchestrate an effective response. As a result, Tcore varies directly with ambient conditions and is frequently outside the optimal range of normothermia.[3] This dysfunction is more prevalent in persons with SCI above T6 (Hi-SCI) because control of vasomotor and sudomotor function has been de-centralized in greater than 60% of the body’s surface area and the availability of skeletal muscle for shivering and mobility is limited due to paralysis below the neurologic level of lesion (NLI).[2,3,22,25] When in warmer environments or during warmer seasons, the limited ability to dissipate heat from ambient temperature exposure or generated by physical activity results in a predominantly unregulated rise in Tcore and an increased vulnerability to hyperthermia (Tcore ≥38°C).[3,26,27] Hyperthermia can affect central nervous system function, causing impaired cognitive performance, consciousness, blurry vision, nausea, and dizziness.[13,28,29] If unchecked, hyperthermia can lead to heat stroke, causing loss of consciousness, permanent central nervous system damage, and progress to multiple organ system failure and death.[29,30] From 2004 to 2018, a total of 10,527 deaths in the United States resulted from heat exposure.[31] The dangers of

prolonged heat exposure in vulnerable persons were demonstrated by a heat wave that occurred in June 2021 in the Pacific Northwest.[32-34]

Dysfunctional thermoregulation after SCI also affects quality of life (QOL). Heinemann et al. assessed the influence of environmental factors that were perceived as barriers and affected health-related QOL in persons disabled from neurological injuries;[5] 570 participants who suffered a stroke, traumatic brain injury (TBI), or SCI (SCI: n=193) rated the difficulty of 18 perceived barriers in home, outdoor, and community settings. “Feeling too hot or cold outdoors” was the *most* frequently reported barrier of the 18 items, while “feeling hot or cold at home” was the fourth most common barrier. “Feeling too hot or cold in stores” was eighth most common barrier.

When participating in social, religious, or work functions during warmer seasons, persons with SCI frequently find themselves in hot environments for prolonged periods, rapidly progressing from feeling comfortably warm to feeling “overheated” and uncomfortable and at increased risk for heat-related illness. However, interventions addressing thermodysregulation during heat exposure in persons with SCI are limited. Exploration of a safe, efficacious bioengineering intervention that has the potential to minimize the adverse effects of prolonged heat exposure and its negative impact on participation and QOL in Veterans with SCI should be a priority. If efficacious, other vunerable Veteran populations adversely affected by heat exposure, e.g., persons with 3rd degree burns, MS, and aged ≥ 70 years of age, may also benefit from this intervention,

Cooling Interventions to Decrease the Risk of Hyperthermia in Able-Bodied (AB) Persons

Studies in athletes to reduce heat-related illness, increase performance, and control the rise in Tcore during exercise in warm ambient conditions have utilized cooling vests, cold water immersion, ice slurry ingestion, cooling packs, and facial wind and water sprays.[35,36] Investigators have used cooling prior to heat exposure (pre-cooling) to increase heat storage capacity and/or during heat exposure (per-cooling) to limit heat accumulation.[36,37] The cooling vest was found to be most effective during per-cooling due to its ability to cover a large surface area of the body and its practicality. Combining its use to both before and during exercise afforded the greatest cooling effect.[35,38,39]

Cooling Interventions to Decrease the Risk of Hyperthermia in Persons with SCI

Cooling interventions explored in persons with SCI have included hand and foot cooling, water sprays (spray-bottles), and cooling garments (vests, hats, neckbands) primarily during exercise conditions and with varying results.[40-47] An aluminum back plate on a wheelchair cooled by Peltier transformers was developed, but only tested in 5 AB subjects during heat exposure.[48] The most promising of these interventions seems to be the ice vest and water spray on exposed skin, which, when used either before or during exercise in persons with tetraplegia, resulted in Tcore being significantly lower compared to the control condition (exercise with no vest or no water spray).[44,45] Bongers et al. studied use of a cooling vest in persons with low paraplegia during exercise in temperate ambient conditions.[46] They found that the vest improved comfort, lowered skin temperatures, and improved core/skin thermal gradient, but did not prevent the increase in Tcore. However, persons with low paraplegia have greater thermoregulatory capacity than those with Hi-SCI and the vest may have had a greater effect in persons with Hi-SCI during warmer conditions (greater heat load), as evidenced by Trbovich et al. using water spray.[27,49] Webborn et al. compared the use of an ice vest in athletes with tetraplegia during exercise in warm conditions; the vest, either before (20 minutes prior) or during exercise, attenuated the rise in Tcore and improved comfort compared to exercise with no vest.[45]

However, when used outdoors and for longer periods (e.g., outdoor summer travel, social events), there are disadvantages of using a passive ice vest (i.e., replenishing the ice in the vest and the necessity of carrying ice). Similar disadvantages exist with water spray (i.e., having someone assist with spraying and replenishing the water for the spray). The feedback-controlled “smart” cooling vest does not need refilling because it continually cools and recirculates the cooled water for improved heat conduction, its temperature can be controlled, and once wet, the material of the vest will continue to provide evaporative heat loss for 3-4 hours.

3. PROCEDURES, METHODS AND EXPERIMENTAL DESIGN.

Research Design: An exploratory protocol with two phases (AB safety; SCI safety and efficacy) will be performed. In Phase 1, because those with Hi-SCI potentially have impaired or absent skin temperature sensation, AB participants will wear the wet "smart" cooling vest to determine its safety. Phase 2 will be performed for efficacy in a single group of persons with Hi-SCI in a prospective, repeated measures design with two conditions (experimental: *wet vest*, control: *no vest*) administered in random order. The objective of Phase 2 is to determine if persons with Hi-SCI dissipate body heat more effectively in the *wet vest* condition compared to the *no vest* condition as evidenced by a smaller rise in Tcore, a decreased perception of heat, and increased thermal comfort. We expect a mean increase in Tcore of 0.6±0.3°C and a perception of feeling "hot or very hot" in the *no vest* condition, as evidenced in two of our prior studies with identical challenges.[50,51]

Participants: Ten participants with high-level SCI (C4-T2, AIS A & B) and 5 AB participants matched for age (±5 years) and gender will be recruited for study participation.

Participant Recruitment: Patients referred by their physician following routine physical examinations will be approached for potential 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).

Inclusion Criteria:
1. 18-68 years of age
2. SCI >1 year in duration
3. Level of SCI C4-T2, AIS A & B
4. Gender and age-matched (±5 years) AB controls
5. Euhydration (participants will be instructed to avoid caffeine and alcohol, maintain normal salt and water intake and avoid strenuous exercise for 24 hours prior to study).

Exclusion Criteria:
1. known cardiovascular, kidney or untreated thyroid disease
2. traumatic brain injury (mod-severe)
3. diabetes mellitus
4. acute illness or infection
5. broken, inflamed, or otherwise fragile skin
6. pregnancy
7. BMI >30 kg/m^2
8. smoking

Methods: On 3 separate days (Phases 1 & 2), participants will arrive in the laboratory between 8:00-11:00 AM.

Preparation for Study Visits: Participants will be instructed to avoid caffeine and alcohol, maintain normal salt and water intake, and avoid strenuous exercise for 24 hours prior to study on each visit. Participants will wear a T-shirt and shorts during all visits to maximize skin exposure to the warm temperature. The T-shirt will also prevent the cooling vest from directly touching the skin. Each participant will be instructed to eat a light meal (plain bagel or 2 pieces of toast) 2 hours prior to their visit. Participants will be asked to empty their bladders prior to the study visit and again upon arrival, if necessary.

Instrumentation: (*For all participants*) After obtaining informed consent, participants will be instrumented in a thermoneutral room (25°C) and in their wheelchair (Hi-SCI) or a provided wheelchair for AB controls. Participants will remain seated and relatively still but will be instructed to use their pressure relief seat cushion (e.g., Roho) and maintain their usual pressure relief schedule (e.g., weight shifting every 15 minutes). Laser Doppler flowmetry (LDF) will be used to measure changes in microvascular perfusion rate by placing a Doppler probe on the skin of the ventral forearm and calf bilaterally as an index of vascular sympathetic withdrawal. Changes in skin blood flow will assessed from calculations of cutaneous vascular conductance (CVC = LDF/MAP), a more accurate measure of change in skin blood flow.[52,53] An automated blood pressure cuff will be placed above the elbow to measure brachial blood pressure (BP) and heart rate (HR). Sweat rate (SR) will be measured by the Quantitative Sweat Measurement System (WR Medical Electronics, Stillwater, MN) with capsules secured to 4 sites: left

upper arm, left forearm, left mid-thigh, and left midcalf (C5, T1, L3, and L5 dermatomes, respectively). A pulse oximeter will be placed on the second digit to detect blood oxygen saturation. An infrared ear thermometer will be used to assess tympanic temperature.

For AB participants (Visit 1): Skin thermocouples will be secured at 12 sites on the ventral and dorsal torso (mid-clavicular line from T3 to T10 dermatomes, bilaterally) for collection of skin temperatures (Tsk).

For participants with Hi-SCI (Visits 2 & 3): Participants with Hi-SCI will be asked to empty their bladders to minimize risk of AD during the heat stress protocols (*wet vest*, *no vest)*. Skin thermocouples will be secured at 14 sites, 10 skin thermocouples on the ventral and dorsal torso (five on each side) and 4 additional thermocouples on both hands and feet (2 on each side) for distal skin temperatures as an indirect index of sympathetic vasomotor regulation.[55] A disposable forehead skin temperature sensor (Bair Hugger™ Spot On™ Temperature Monitoring System, 3M, Maplewood, Minnesota) will be placed on the orbital bone, above the eyebrow, on whatever side is most comfortable for the participant in order to measure core temperature (Tcore).

Baseline Collection (BL): (for all 3 Visits) At the end of the instrumentation period (~30 minutes) at 25°C while seated and wearing only shorts and a standard T-shirt, a baseline (BL) collection of the following parameters will be performed for 15 minutes. Tcore (in persons with Hi-SCI only) and Tsk will be measured continuously. Subjective ratings of thermal sensation, assessed on a 9-point scale (TS) and general thermal comfort on a 6-point scale (TC).[56] HR, BP, blood oxygen saturation, tympanic temperature and 5 minutes of LDF will be measured at 10-minute intervals. BP will be assessed immediately pre and post each LDF interval for calculation of CVC.[57,58] SR will be measured for 15 minutes continuously.

1. Thermal Challenge for Safety and Comfort Study (**Phase 1**; 1 visit, AB participants only): AB participants will be fitted with an appropriately sized cooling vest while seated in a wheelchair at the end of BL. Participants will be transferred into a pre-heated (35°C, 35% relative humidity) thermal chamber for 2 hours with the wet cooling vest on full power. Skin temperatures will be continuously measured at multiple sites under the vest. TC and TS will be assessed every 10 minutes. Participants will be queried if they feel any areas of cold-related discomfort or numbness (cold spots), or any other feelings of discomfort from the vest. LDF will be measured as above, but at 20-minute intervals. SR will be measured for 15 minutes every 30 minutes (4 times). HR, BP, blood oxygen saturation and tympanic temperature will be assessed at 10-minute intervals. **Determinants of success for Phase 1:** 1) Skin thermocouple temperatures maintained ≥20 °C, and 2) subjective ratings of TS not less than “cool” (i.e., not “cold” or “very cold”) on the 9-point TS scale.

2. Thermal Challenge with Wet Cooling Vest vs. No Vest (**Phase 2**; 2 visits, participants with Hi-SCI only): After 15 minutes of baseline data collection in a thermoneutral environment (25°C), participants with HI-SCI will be fitted with an appropriately sized cooling *wet vest* or will wear *no vest* (in random order). To provide evaporative heat loss, the vest material will be saturated with water using a spray bottle. Participants will then be transferred into a warm (35°C, 35% relative humidity) thermal chamber for up to 2 hours. Tcore (Bair Hugger™ Spot On™ forehead skin sensor) and Tsk (thermocouples at multiple sites under the vest and on hands and feet) will be measured continuously; subjective TS and TC will be measured at 10-minute intervals; LDF will be measured as above (for CVC) at 20-minute intervals. SR will be measured for 15 minutes every 30 minutes (4 times). HR, BP, blood oxygen saturation, and tympanic temperature will be measured at 10-minute intervals for vital signs’ information. Participants will be queried if they have any feelings of discomfort. If the participant’s Tsk underneath the vest falls below 20°C, or Tcore rises to 38°C, and/or the participant requests study termination because of discomfort, the vest will be removed, the heat challenge will be immediately terminated, and the participant will be transferred to a cool environment, covered with cool blankets, as appropriate, and provided cold liquids. The study physician will be directly responsible for subjects’ medical safety during study protocols. Subjects’ Tcore, HR and BP, will be monitored at frequent intervals. Symptoms suggestive of AD or hyperthermia will be assessed every 10 minutes. The study physician will be notified immediately of any symptoms or signs of concern. Subjects will be medically evaluated promptly, and the study terminated if any safety issues arise. Subjects will be monitored for at least 30 minutes of recovery to ensure Tcore returns to within 1% of BL value.

Determinants of Efficacy Failure or Success for Phase 2: 65% of participants in the *wet vest* condition will have a significantly reduced elevation in Tcore (≤0.3°C), and 2) a greater percentage will report increased thermal comfort (decreased perception of feeling "hot", "very hot", or "uncomfortable") compared to the expected increase in Tcore of 0.6°C and reported thermal comfort in the *no vest* condition.

Outcome Variables: **Phase 1**: Skin thermocouple temperatures, ratings of thermal comfort and sensation, cold spots, and any reported physical discomfort from the vest. **Phase 2**: The primary endpoint will be the magnitude and rapidity of the rise in Tcore upon exposure to a warm environment. The perception of thermal comfort and sensation of heat will be obtained as secondary endpoints.

Procedures: **Thermoregulatory Measurement Procedures**: The following measurements will be obtained during BL and Thermal Challenge for all visits (**Table 1**). *Tcore:* will be monitored by a disposable forehead skin temperature sensor (Bair Hugger™ Spot On™ Temperature Monitoring System, 3M, Maplewood, Minnesota) in persons with Hi-SCI only. *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 12 sites on the anterior and dorsal trunk of the participant. *Microvascular Perfusion (LDF):* will be measured using laser probes on the skin of both ventral forearms and calves with a Periflux System 5000 Laser Doppler (Perimed, Stockholm, Sweden) for calculation of CVC. *Sweat rate (SR):* will be measured by the Quantitative Sweat Measurement System (WR Medical Electronics, Stillwater, MN) with capsules secured to 4 sites: left upper arm, left forearm, left mid-thigh, and left midcalf.

Table 1: Schedule of Assessments and Procedures

Measures	Acclimation	BL	Heat
Run Time (min)	30	15	120
Cumulative Time (min)	30	45	165
*Tcore		††	††
Skin Temperatures		††	††
*Sweat Rate		1x	4x
Thermal Sensation	1x	2x	12x
Thermal Comfort	1x	2x	12x
Laser Doppler Flow		2x	6x
Brachial BP, O2 sat		2x	12x

†† Tcore and skin temperature measurements will be monitored and collected simultaneously throughout the study. *Tcore and Sweat Rate in persons with Hi-SCI only.

Thermal Sensation (TS) and Thermal Comfort (TC): TS will be measured by a 9-point thermal sensation scale, while TC will be measured by a 6-point thermal comfort scale (attached).[56] Tympanic temperature will be assessed in all participants using a Braun PRO 6000 infrared ear thermometer (Welch Allyn, Skaneateles Falls, NY).

Hemodynamic Measurement Procedures: Brachial BP: BP will be measured at the brachial artery using the Carescape Dinamap V100 Automated BP Monitor (Carescape, Milwaukee, WI). BP will be obtained at 10-minute intervals throughout BL and Thermal Challenge and immediately pre and post LDF measurement for calculation of CVC.

***Sample Size and Statistical Approach*:** We are hypothesizing that after 2 hours of heat exposure, the average increase in Tcore of persons with Hi-SCI with the wet cooling vest will be 0.3±0.3°C compared to an increase of 0.6±0.3°C (data from our prior study using an identical heat challenge, but with no vest).[51] Therefore, a sample size of 10 participants would be needed to achieve a power of 81% for a two-sided, one-sample analysis at an alpha of 0.05. For Phase I (safety), descriptive statistics will be used to determine the number of participants who have a vest failure. Vest failure will be defined as any area of skin under the vest (Tsk) with a temperature <20°C and/or the number of participants who report a TS of "cold" or "very cold". For efficacy testing, a 2 x 2 (condition, time) repeated measures ANOVA will be used to determine significant main or interaction effects. If main or interaction effects are determined, post hoc analysis will be performed using t-tests or appropriate non-parametric tests to determine significant differences between conditions. Significance will be set at an alpha level of 0.05.

3a. Basic Information - Even if described under "Procedures", list the following information, where pertinent:

3a. i) Procedures to be used (e.g., biopsy, surgical operation, interview, experimental diet, infusion, drug administration, etc.) and with what frequency?

Procedures

Thermoregulatory Measurement Procedures: The following measurements will be obtained during BL and Thermal Challenge for all visits (**Table 1**).

Tcore: will be monitored by an disposable forehead skin temperature sensor(Bair Hugger™ Spot On™ Temperature Monitoring System, 3M, Maplewood, Minnesota)in persons with Hi-SCI only.

In all participants:
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 12 sites on AB controls and 14 sites – 10 sites on the chest/abdomen (five on each side) and 4 sites on the bilateral hands and feet (2 on each side) on persons with Hi-SCI.
Sweat rate measurement (QS): will be measured for 15 minutes, once during the baseline period and 4 times during the thermal challenge at 30-minute intervals, for a total of 5 measurements.
Microvascular Perfusion (LDF): will be measured using laser probes on the skin of both ventral forearms and calves with a Periflux System 5000 Laser Doppler (Perimed, Stockholm, Sweden) for calculation of CVC.
Thermal Sensation (TS) and Thermal Comfort (TC): TS will be measured by a 9-point thermal sensation scale, while TC will be measured by a 6-point thermal comfort scale.[56]
Tympanic temperature will be assessed using a Braun PRO 6000 infrared ear thermometer (Welch Allyn, Skaneateles Falls, NY).

Hemodynamic Measurement Procedures:
Brachial BP: BP will be measured at the left brachial artery using the Carescape Dinamap V100 Automated BP Monitor (Carescape, Milwaukee, WI). BP will be obtained at 10-minute intervals throughout BL and Thermal Challenge.
Blood Oxygen Saturation: Blood oxygen saturation will be recorded every 10 minutes.

3a. ii) Description of procedures. If pharmacologic agents or radioisotopes are to be administered, provide dosages, mode of administration and duration of usage.

Core temperature measurement (Tcore): will be monitored by an disposable forehead skin temperature sensor, (Bair Hugger™ Spot On™ Temperature Monitoring System, 3M, Maplewood, Minnesota) in persons with Hi-SCI only.
Skin temperature measurement (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 12 sites under the vest on the anterior and dorsal trunk of AB participants on AB controls and 14 sites – 10 on the anterior and dorsal trunk and 4 on both hands and feet- on persons with Hi-SCI.
Microvascular Perfusion (LDF): will be measured using laser probes on the skin of both ventral forearms and calves with a Periflux System 5000 Laser Doppler (Perimed, Stockholm, Sweden) for calculation of CVC.
Sweat rate (SR): will be measured by the Quantitative Sweat Measurement System (WR Medical Electronics, Stillwater, MN) with capsules secured to 4 sites: left upper arm, left forearm, left mid-thigh, and left midcalf (C5, T1, L3, and L5 dermatomes, respectively).
Brachial BP & HR: will be measured at the brachial artery using the Carescape Dinamap V100 Automated BP Monitor (Carescape, Milwaukee, WI) placed above the left elbow.
Thermal Sensation (TS): TS will be measured by a 9-point thermal sensation scale (attached).
Thermal Comfort (TC): TC will be measured by a 6-point thermal comfort scale (attached).
Tympanic temperature will be assessed using a Braun PRO 6000 infrared ear thermometer (Welch Allyn, Skaneateles Falls, NY), along with other vital signs, e.g., BP, HR, O2 sat.

3a. iii) Population to be studied, listing basis for selection or exclusion and number to be studied.

Participants: Ten participants with high-level SCI (Hi-SCI: >T6) and 5 able-bodied (AB) participants matched for age (±5 years) and gender will be recruited for study participation. All subjects will be studied at the James J. Peters VA Medical Center, Bronx, NY.

Participant Recruitment: Patients referred by their physician following routine physical examinations will be approached for potential 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).

Inclusion Criteria:
1. 18-68 years of age
2. SCI >1 year in duration.
3. Level of SCI C4-T2, AIS A & B
4. Gender and age-matched (±5 years) AB controls
5. Euhydration (participants will be instructed to avoid caffeine and alcohol, maintain normal salt and water intake and avoid strenuous exercise for 24 hours prior to study).

Exclusion Criteria:
1. known cardiovascular, kidney or untreated thyroid disease;
2. traumatic brain injury (mod-severe)
3. diabetes mellitus;
4. acute illness or infection;
5. broken, inflamed, or otherwise fragile skin;
6. pregnancy;
7. BMI >30 kg/m^2;
8. smoking;

3a. iv) If subjects are patients, will conventional therapy or diagnostic procedures be withheld or modified for the purpose of this study?
No. Conventional therapy or diagnostic procedures will not be withheld or modified for the purpose of this study.

3b. Multi-Site Studies
Not applicable.

3c. Possible Risks
3c. i) List possible hazards to subjects and/or investigative personnel from the procedures, drugs, or isotopes to be employed. What monitoring or other safety precautions will be taken?

Thermoregulatory Measurement Procedures
Skin Temperature Monitoring (Tsk): Skin temperature measurement is non-invasive & not associated with risks. However, persons with sensitive skin could find the tape used to secure the thermocouple to be irritating.
Core Temperature Monitoring (Tcore): The Bair Hugger™ Spot On™ Temperature Monitoring System is non-invasive & not associated with risks. However, persons with sensitive skin could find the thermocouple adhesive to be irritating. Tcore measurement will be performed in subjects with Hi-SCI only (Visits 2 & 3).
Tympanic temperature: is non-invasive and a disposable sleeve is used for each subject. The placement of the ear thermometer may feel uncomfortable.
Sweat rate (SR) is non-invasive & not associated with risks. However, persons with sensitive skin may find the tape used to secure the capsules to the skin to be irritating.
Thermal Sensation: is non-invasive & not associated with any risks.
Thermal Comfort: is non-invasive & not associated with any risks.

Hemodynamic Measurement Procedures
Microvascular Perfusion: Microvascular Perfusion (LDF) measurement is a non-invasive measurement and is not associated with risks.
Brachial Blood Pressure (BP) and Heart Rate (HR): Brachial BP and HR measurement is non-invasive & not associated with risks. The subject may feel the pressure of the inflated cuff to be uncomfortable.

Thermal Challenge
Hyperthermia: A potential risk to subjects is an increase in Tcore ≥ 38.0°C causing hyperthermia secondary to sitting in a warm thermal chamber at 35.0°C for up to 2 hours. This risk is greater in persons with higher levels of SCI compared to AB controls. The risk of hyperthermia will be minimized in all subjects by

monitoring Tcore continuously throughout the study. Should the subjects' Tcore reach 37.9°C, or if they complete 120 minutes in the warm thermal room, the protocol will be terminated, and subjects will be transferred to a cooler environment (22°C), covered with cool, wet blankets, and given cold liquids. Subjective symptoms of hyperthermia (headache, confusion, dizziness, nausea, feeling faint, etc.) and autonomic dysreflexia (AD) (increased BP, pounding headache, etc.) will also be assessed throughout the procedure, and if subjects are deemed at risk of hypothermia or AD, the protocol will also be terminated. To decrease the risk of AD, participants with SCI will be asked to empty their bladder prior to starting the protocol.

There is a slight risk of heat-induced hypotension. This risk is greater in AB persons because their ability to peripherally vasodilate, in response to heat, remains intact as opposed to their SCI counterparts. This risk will be minimized by monitoring for symptoms of hypotension (systolic blood pressure (SBP) decrease >20 mmHg from baseline levels, dizziness, lightheadedness, etc.) throughout the procedure and if subjects are deemed at risk of hypotension, the protocol will be terminated.

Cooling Vest: There is a slight risk of the wet cooling vest irritating the skin. This risk will be minimized by instructing the subject to wear a standard T-shirt between the vest and their bare skin. Another potential risk to subjects is non-freezing cold injury due to wearing the cooling vest for a duration of 2 hours. The risk of non-freezing cold injury is greater in subjects with HI-SCI who have insentient skin. To minimize this risk, all subjects will wear a T-shirt under the vest and safety testing will first be conducted on AB subjects who will be able to determine if the sensation at any time is less (colder) than "cool". If the vest is judged to be "cold" or any area of the vest is "cold", the vest will be promptly removed, and technical adjustments will be made for safety. Only after safety is confirmed in AB subjects, will the vest be used in subjects with HI-SCI. The vest will self-regulate using feedback from multiple sensors to keep any material within its interior surface well above 17°C, which is the threshold necessary to cause a non-freezing cold injury with prolonged exposure. In an abundance of caution, the minimal vest temperature will be limited to ≥20°C. The risk of non-freezing cold injury will also be minimized by constant monitoring of skin temperature under the vest by use of skin thermocouples (12 sites in AB, 10 in Hi-SCI). If the temperature under the vest is determined to be <20°C, the vest will be promptly removed, and the protocol will be terminated. The risk of non-freezing cold injury to the skin is minimized as the vest will have been fully bench-tested to meet all safety requirements before human subject testing.

Subject modesty: Subjects will wear minimal clothing (shorts and T-shirt) during the study to maximize bare skin exposure to the warm temperature. The exposure may exceed the subject's modesty causing potential embarrassment. To minimize this risk, exposure will be limited to the area of the thermal chamber only and to the minimum number of research team members necessary.

Additional unforeseen risks will be minimized by obtaining and reviewing a thorough medical history of prospective participants. Subjects and clinical experts will have the study objectives explained in detail and will be given the opportunity to ask questions about research procedures and the implications of the research. Moreover, study coordinators will be carefully selected that have experience in working with patients with SCI and have formed a good rapport with these individuals. In addition, we have structured the questionnaire to avoid questions about income and service connection, which have raised subject concerns in previous studies (where veterans refused to answer).

3d. Possible Benefits

There may be no direct benefit to the subject for participating in this study. However, if an abnormality is identified during the study, it will be brought to the attention of the subject and the subject's physician. The information which is obtained may be useful scientifically and clinically helpful to others. If the self-regulating cooling vest proves to be an effective treatment for maintenance of Tcore during warm temperature exposure in this study, it or a similar device may be considered as an intervention to address thermodysregulation following a spinal cord injury.

4. PREVIOUS WORK DONE BY YOU OR YOUR COLLABORATORS ON THIS OR RELATED PROJECTS, LISTING PUBLICATIONS

Preliminary Studies

We have shown that 8 persons with tetraplegia (NLI C5-C7, ASIA Impairment Scale [AIS] A-B) exposed to warm temperatures (35°C) for ~2 hours had a significantly greater rise in Tcore than 9 matched controls

(0.8±0.3°C vs -0.06±0.2°C; p<0.001, respectively).[50] Interruption of sympathetic pathways for control of heat dissipating mechanisms was supported by significantly lower plasma NE levels (p<0.001) in the tetraplegic group compared to controls during BL and after Heat Challenge conditions. Subjective thermal sensation was rated as “hot” to “very hot” after 2 hours of challenge but was not significantly different than that of controls.[50]

In 20 persons with Hi-SCI (NLI C4-T4, AIS A-B) who were exposed to the identical warm challenge, we found a greater rise in average Tcore than 19 matched AB controls (0.6±0.3°C vs. -0.1±0.2°C, p<0.001, respectively). Thirteen of the 20 (65%) had evidence of greater sympathetic interruption (lower blood pressure and sweat rate than controls) and demonstrated a greater rise in Tcore than 7 persons (35%) with Hi-SCI (0.8±0.3°C vs. 0.3±0.3°C; p<0.001, respectively) whose blood pressure and sweat rate were not different than controls, despite NLI and AIS grades not being significantly different between the two Hi-SCI groups.[51] The lower blood pressure and decreased sweat rate in 13/20 participants with Hi-SCI signify greater vasomotor disruption, greater sympathetic cholinergic interruption, and the least amount of evaporative heat loss. In support of the significance of these findings in achieving optimal health and QOL, our lab conducted a study assessing subjective comfort during the warmer seasons, which surveyed 100 participants with SCI (50 persons with tetraplegia (C3-C8, AIS A-D), 50 with paraplegia (T1-T12, AIS A-D), and 50 age-matched AB controls (unpublished data). Both tetraplegia and paraplegia groups reported an impaired ability to stay comfortable when compared to the AB group. The negative effect on social activities was greatest in the tetraplegia group. In addition, once feeling overheated, a greater proportion of the participants in the tetraplegic group reported needing significantly more time (≥20 minutes) to return to feeling comfortable than those in either the paraplegic or AB groups.

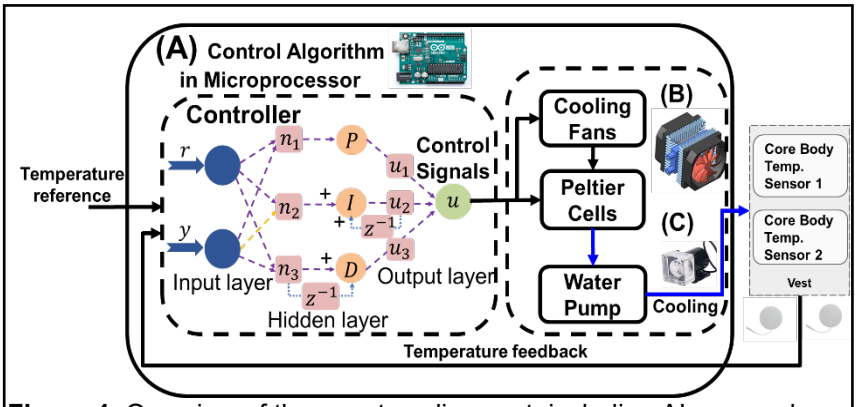
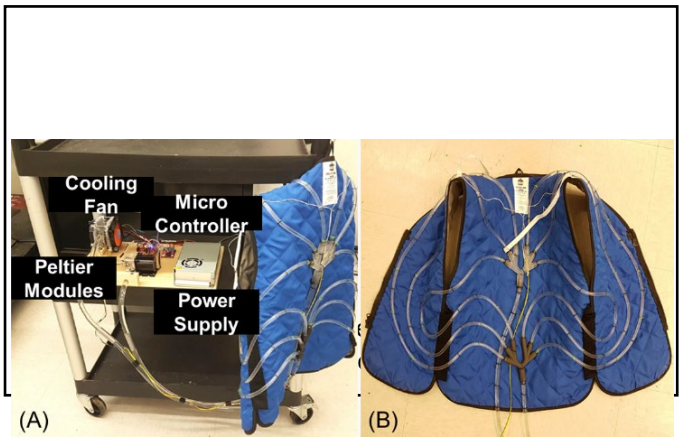


Figure 1. Overview of the smart cooling vest, including AI powered controller, electrical circuits (black lines) and fluid pathways (blue lines).

Our “smart” cooling vest is designed to provide a large area of contact with the user with a material that is a good thermal conductor and will be maintained at a uniform temperature 10-15°C cooler than the user’s skin temperature beneath the vest. It can automatically regulate temperature by closed-loop control through processing skin temperature and Tcore for safety and efficacy. The vest is novel as it is electrically powered, utilizing a lightweight transformer to thermoelectrically cool water (i.e., Peltier thermal effect), and a low-power turbine to pump the cooled water through a web of thin-walled plastic tubes embedded in the vest (**Figure 1**: **(A)** Arduino (microprocessor), **(B)** two Peltier transformers with heat sinks and cooling fans, and **(C)** centrifugal water pump (turbine).



The thermoregulation program of the VA RR&D Center for the Medical Consequences of Spinal Cord Injury and Dr. Hao Su, Picasso Intelligence L.L.C. have developed an initial prototype of a feedback-controlled cooling vest specifically designed for persons with SCI with an impaired ability to dissipate heat (**Figure 2).**

The turbine has a much smaller power requirement (9.6 watts) than each Peltier transformer (60 watts) and, thus, can be run at maximum speed whenever cooling is powered on to maintain the circulation of cooled water. The cold side of each transformer is attached to a water block to cool the returning warmed water entering the block. The heat side of each transformer has an aluminum heat sink and a cooling fan capable of removing large amounts of heat from the module (**Figure 3**). Cooled water from the transformers is pumped by the turbine into six individual tubes. The tubes circulate cooled water through the vest before entering a second junction that merges them into one tube for return of the warmed water to the water block for re-cooling. PVC tubes (6.25 mm in diameter) were chosen for their higher thermal conductivity as compared to other plastic tubing. The tubes were sewn into the inside surface of the vest.

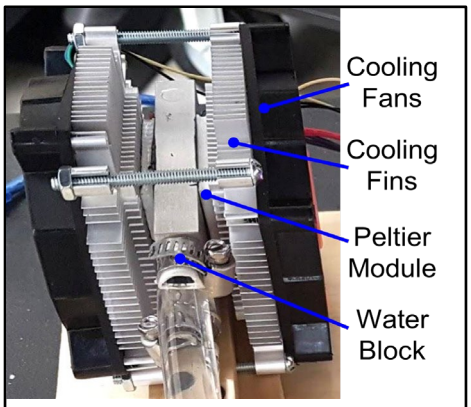


Figure 3. Thermoelectric Peltier cooler with water block, cooling fans, and cooling fins.

The vest material is a lightweight, absorbent polymer that, if saturated with water, will use evaporation to provide additional heat loss over several hours (3-4 hrs). Most cooling vests are passive and use either conduction or evaporation to dissipate body heat. Our vest is designed to have the potential to selectively use either or both to restore some of the interrupted thermoregulatory function of conduction (vasodilation) and evaporation (sweating) in Veterans with Hi-SCI to optimize heat dissipation during ambient heat exposure. The inner lining of the vest is a thin, water-resistant material designed to minimize the user's clothing from getting wet. The large surface area of the cooling vest is designed to provide a sufficient interface for heat exchange to increase the rate of heat conduction from core to skin by lowering the expected skin temperature (~35ºC) during heat challenge. Lowering skin temperature by 10-15ºC serves to increase the temperature gradient between core and skin to increase the rate of heat dissipation from the body. The cool vest also functions as an insulator, preventing ambient heat from conducting heat into the user's torso.

Temperature Regulation with Feedback Control: Suzurikawa et al. studied a "body heat removal system" utilizing thermo-electric cooling intended for persons with SCI and tested it in 5 AB participants.[48] However, their device did not use closed-loop temperature control, only cooled the back, and they did not report further testing in persons with SCI. Power for our "smart" vest is modulated by a closed-loop feedback control loop to increase safety and efficacy. The microprocessor receives Tcore information from thermistor sensors taped to both axillae and skin temperature information from thermistor sensors taped to areas of the trunk with the greatest contact with the cool vest. Axillary measurements of Tcore are reliable and typically 1ºC less than rectal measurement.[59,60] Therefore, Tcore values of ≥36.6ºC and ≤35.4ºC will be used as thresholds to power on or off the vest, respectively. Threshold Tcore temperature values can also be manually entered, e.g., ±0.5 ºC from the user's measured baseline Tcore. Skin temperature values of >33ºC and <20ºC will be used to power on and power off the vest, respectively. Sensors monitoring circulating water temperature will also feed information to the microprocessor. All thermistors assess temperature every 5 seconds and information sent to the microprocessor is filtered to provide a moving average of the last ten measurements. The skin temperature threshold of <20ºC to power off the vest will override Tcore temperature to protect the skin from non-freezing cold injury, a safety feature designed to prevent non-freezing cold injury (skin temperatures < ~17°C for prolonged periods)[61] in persons with Hi-SCI who have insentient skin below their level of injury.[1-3]

The current prototype of the vest possesses the key features of the hardware and software requirements to sense and control human body temperatures (**Figure 2**). We will optimize the current prototype to develop a new version of the vest (Prototype II) by incorporating more powerful Peltier transformers (40 Watt of the current prototype to 60 Watt for Prototype II) for a larger range of temperature control (0-5°C of current prototype to 10-15°C), a larger web of thin-walled plastic tubes to increase contact area for heat conduction, improved feedback control of body temperature to minimize response delay (e.g., thermal regulation of body temperature usually takes several minutes to respond to external control), and validation of safety mechanisms. Dr. Su will direct an engineer at Picasso Intelligence to leverage Artificial Intelligence (AI)-powered optimal control algorithms to rapidly determine control parameters to maintain the desired Tcore. The AI-based neural network controller will improve both transient response and steady-state response of the temperature control system which typically involves time delay in temperature response.[62] The neural network-based controller will perform adaptive control through learning processes to

overcome the time delay of temperature response. The control algorithm (implemented on a microprocessor with real-time control (A in Fig. 1) will have a three-layer neural network,[62] including a hidden layer, thus combining the advantages of the standard proportional–integral–derivative (PID) control and a self-learning neural network. The input of the neural network includes reference temperature and body temperature sensor information. The three outputs of the hidden layer will be set as proportional P, integral I, and derivative units D, respectively. During system operation, the neural network is online-trained to automatically adjust the control parameters (P, I, D). The neural network will be able to learn the controller parameters (PID), resulting in more individualized thermal regulation for different users. Dr. Su is experienced in human-in-the-loop control of human bio-systems, demonstrated by optimizing human performance with reinforcement learning-based optimal control algorithms.[63] Picasso Intelligence will follow FDA guidelines for bench testing of medical devices to assess the performance of Prototype II. Key criteria include 1) accuracy of Tcore and skin temperature measurement (within 1°C), 2) responsiveness of closed-loop control (within 1°C), mass within 5 kg (target weight, 2.9 kg).

5. SIGNIFICANCE OF THIS RESEARCH.

Incidence & Prevalence of SCI: In the US alone, the estimated occurrence of new SCI is 18,000 cases each year with approximately 299,000 people currently living with SCI. Average lifetime costs for medical care and living expenses for a person with incomplete tetraplegia, the most common neurological form of SCI, is approximately 4 million dollars.[64] In addition, SCI is one of the most labor-intensive and expensive chronic conditions to the Veterans Health Care Administration (VHA).[65]

Significance of Current Research: Current clinical recommendations for persons with SCI during hot weather are quite general: avoid direct sunlight, dress sparingly, drink plenty of fluids, and stay indoors during midday on hot, humid days. There are also no standardized interventions that have been proven to stabilize Tcore during heat exposure after SCI. The **goals** of this proof-of-concept pilot study are: 1) to refine the current prototype to meet bench standards prior to human testing; 2) determine the safety and tolerability of a feedback-controlled “smart” cooling vest using able-bodied (AB) controls; and 3) to determine the efficacy of the wet “smart” cooling vest to maintain Tcore (within 0.3°C) and improve thermal comfort in participants with Hi-SCI during 2 hours of controlled warm environment (35°C). If efficacious, we intend to submit a full Merit Review application to collaborate with the Human Engineering Research Laboratory (HERL: letter of support provided by Dr. Rory Cooper, Director of HERL) to make the vest more appropriate for home testing to determine effectiveness in improving societal participation and QOL in Veterans with SCI during warmer seasons, residing in or traveling to hot climate zones. We will request the assistance of the VA’s Technology Transfer Program to successfully commercialize a safe and practical cooling vest for vulnerable individuals.

LIST OF KEY BIBLIOGRAPHIC REFERENCES

1. Downey JA, Huckaba CE, Myers SJ, Darling RC. Thermoregulation in the spinal man. *J. Appl. Physiol.* 1973;34(6):790-794.

2. Guttmann L, Silver J, Wyndham CH. Thermoregulation in spinal man. *J. Physiol.* 1958;142(3):406-419.

3. Price MJ, Trbovich M. Thermoregulation following spinal cord injury. *Handb. Clin. Neurol.* 2018;157:799-820.

4. Wecht JM, La Fountaine MF, Handrakis JP, West CR, Phillips A, Ditor DS, Sharif H, Bauman WA, V. KA. Autonomic Nervous System Dysfunction Following Spinal Cord Injury: Cardiovascular, Cerebrovascular, and Thermoregulatory Effects. *Curr Phys Med Rehabil Rep.* 2015;3:197-205.

5. Heinemann AW, Lai JS, Wong A, Dashner J, Magasi S, Hahn EA, Carlozzi NE, Tulsky DS, Jerousek S, Semik P, Miskovic A, Gray DB. Using the ICF's environmental factors framework to develop an item bank measuring built and natural environmental features affecting persons with disabilities. *Qual. Life Res.* 2016;25(11):2775-2786.

6. Handrakis JP, Rosado-Rivera D, Singh K, Swonger K, Azarelo F, Lombard AT, Spungen AM, Kirshblum SC, Bauman WA. Self-reported effects of cold temperature exposure in persons with tetraplegia. *J. Spinal Cord Med.* 2017;40(4):389-395.

7. Trbovich M, Ford A, Wu Y, Koek W, Wecht J, Kellogg D, Jr. Correlation of neurological level and sweating level of injury in persons with spinal cord injury. *J. Spinal Cord Med.* 2020:1-8.

8. Teasell RW, Arnold JM, Krassioukov A, Delaney GA. Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system after spinal cord injury. *Arch. Phys. Med. Rehabil.* 2000;81(4):506-516.

9. Krassioukov A, Stillman M, Beck LA. A Primary Care Provider's Guide to Autonomic Dysfunction Following Spinal Cord Injury. *Top Spinal Cord Inj Rehabil.* 2020;26(2):123-127.

10. Wecht JM, Harel NY, Guest J, Kirshblum SC, Forrest GF, Bloom O, Ovechkin AV, Harkema S. Cardiovascular Autonomic Dysfunction in Spinal Cord Injury: Epidemiology, Diagnosis, and Management. *Semin. Neurol.* 2020;40(5):550-559.

11. Greaney JL, Kenney WL, Alexander LM. Sympathetic regulation during thermal stress in human aging and disease. *Auton. Neurosci.* 2016;196:81-90.

12. Guyton A, Hall J. Metabolism and Temperature Regulation. *Textbook of Medical Physiology* 12th Edition ed. Philadelphia, PA: Saunders Elsevier; 2011:867-875.

13. Sessler DI. Thermoregulatory defense mechanisms. *Crit. Care Med.* 2009;37(7 Suppl):S203-210.

14. Fealey RD. Interoception and autonomic nervous system reflexes thermoregulation. *Handb. Clin. Neurol.* 2013;117:79-88.

15. Gordon CJ. Autonomic Nervous System: Central Thermoregulatory Control. *Encyclopedia of Neuroscience.* 2009:891-898.

16. Johnson JM, Kellogg DL, Jr. Thermoregulatory and thermal control in the human cutaneous circulation. *Front Biosci (Schol Ed).* 2010;2:825-853.

17. Morrison SF, Nakamura K. Central neural pathways for thermoregulation. *Front Biosci (Landmark Ed).* 2011;16:74-104.

18. Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J Appl Physiol (1985).* 2010;109(4):1221-1228.

19. Smith CJ, Johnson JM. Responses to hyperthermia. Optimizing heat dissipation by convection and evaporation: Neural control of skin blood flow and sweating in humans. *Auton. Neurosci.* 2016;196:25-36.

20. Downey JA, Huckaba CE, Kelley PS, Tam HS, Darling RC, Cheh HY. Sweating responses to central and peripheral heating in spinal man. *J. Appl. Physiol.* 1976;40(5):701-706.

21. Griggs KE. *Thermoregulatory responses of athletes with a spinal cord injury during rest and exercise.*: Centre for Disability Sport, Loughborough University; 2016.

22. Handrakis JP, Liu SA, Rosado-Rivera D, Krajewski M, Spungen AM, Bang C, Swonger K, Bauman WA. Effect of Mild Cold Exposure on Cognition in Persons with Tetraplegia. *J. Neurotrauma.* 2015;32(15):1168-1175.

23. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, Johansen M, Jones L, Krassioukov A, Mulcahey MJ, Schmidt-Read M, Waring W. International standards for neurological classification of spinal cord injury (Revised 2011). *The Journal of Spinal Cord Medicine.* 2011;34(6):535-546.

24. Franz S, Kirshblum SC, Weidner N, Rupp R, Schuld C, group Es. Motor levels in high cervical spinal cord injuries: Implications for the International Standards for Neurological Classification of Spinal Cord Injury. *J. Spinal Cord Med.* 2016;39(5):513-517.

25. Wecht JM, Krassioukov AV, Alexander M, Handrakis JP, McKenna SL, Kennelly M, Trbovich M, Biering-Sorensen F, Burns S, Elliott SL, Graves D, Hamer J, Krogh K, Linsenmeyer TA, Liu N, Hagen EM, Phillips AA, Previnaire JG, Rodriguez GM, Slocum C, Wilson JR. International Standards to document Autonomic Function following SCI (ISAFSCI): Second Edition. *Top Spinal Cord Inj Rehabil.* 2021;27(2):23-49.

26. Griggs KE, Havenith G, Price MJ, Goosey-Tolfrey VL. Evaporative heat loss insufficient to attain heat balance at rest in individuals with a spinal cord injury at high ambient temperature. *J Appl Physiol (1985).* 2019;127(4):995-1004.

27. Griggs KE, Leicht CA, Price MJ, Goosey-Tolfrey VL. Thermoregulation during intermittent exercise in athletes with a spinal-cord injury. *Int. J. Sports Physiol. Perform.* 2015;10(4):469-475.

28. Simmons SE, Saxby BK, McGlone FP, Jones DA. The effect of passive heating and head cooling on perception, cardiovascular function and cognitive performance in the heat. *Eur. J. Appl. Physiol.* 2008;104(2):271-280.

29. Walter EJ, Carraretto M. The neurological and cognitive consequences of hyperthermia. *Crit. Care.* 2016;20(1):199.

30. Pease S, Bouadma L, Kermarrec N, Schortgen F, Regnier B, Wolff M. Early organ dysfunction course, cooling time and outcome in classic heatstroke. *Intensive Care Med.* 2009;35(8):1454-1458.

31. Vaidyanathan A, Malilay J, Schramm P, Saha S. Heat-Related Deaths - United States, 2004-2018. *MMWR Morb. Mortal. Wkly. Rep.* 2020;69(24):729-734.

32. Olmos S, Choi-Schagrin W, Hubler S. Heat-Related Death Toll Climbs to Nearly 100 in Washington State and Oregon. *The New York Times.* July 2,2021, 2021;U.S. News.

33. Newburger E. Historic heat wave linked to hundreds of deaths in Pacific Northwest and Canada. 2021; https://www.cnbc.com/2021/07/01/heat-wave-linked-to-hundreds-of-deaths-in-pacific-northwest-canada-.html. Accessed July 1, 2021.

34. Popovich N, Choi-Schagrin W. Hidden Toll of the Northwest Heat Wave: Hundreds of Extra Deaths. *The New York Times.* August 11, 2021, 2021;Climate and Environment.

35. Bongers CC, Hopman MT, Eijsvogels TM. Cooling interventions for athletes: An overview of effectiveness, physiological mechanisms, and practical considerations. *Temperature.* 2017;4(1):60-78.

36. Bongers CC, Thijssen DH, Veltmeijer MT, Hopman MT, Eijsvogels TM. Precooling and percooling (cooling during exercise) both improve performance in the heat: a meta-analytical review. *Br. J. Sports Med.* 2015;49(6):377-384.

37. Douzi W, Dupuy O, Theurot D, Smolander J, Dugue B. Per-Cooling (Using Cooling Systems during Physical Exercise) Enhances Physical and Cognitive Performances in Hot Environments. A Narrative Review. *Int. J. Environ. Res. Public Health.* 2020;17(3).

38. Cuttell SA, Kiri V, Tyler C. A Comparison of 2 Practical Cooling Methods on Cycling Capacity in the Heat. *J Athl Train.* 2016;51(7):525-532.

39. Duffield R, Steinbacher G, Fairchild TJ. The use of mixed-method, part-body pre-cooling procedures for team-sport athletes training in the heat. *J. Strength Cond. Res.* 2009;23(9):2524-2532.

40. Griggs KE, Price MJ, Goosey-Tolfrey VL. Cooling athletes with a spinal cord injury. *Sports Med.* 2015;45(1):9-21.

41. Goosey-Tolfrey V, Swainson M, Boyd C, Atkinson G, Tolfrey K. The effectiveness of hand cooling at reducing exercise-induced hyperthermia and improving distance-race performance in wheelchair and able-bodied athletes. *J. Appl. Physiol.* 2008;105(1):37-43.

42. Hagobian TA, Jacobs KA, Kiratli BJ, Friedlander AL. Foot cooling reduces exercise-induced hyperthermia in men with spinal cord injury. *Med. Sci. Sports Exerc.* 2004;36(3):411-417.

43. Webborn N, Price MJ, Castle P, Goosey-Tolfrey VL. Cooling strategies improve intermittent sprint performance in the heat of athletes with tetraplegia. *Br. J. Sports Med.* 2010;44(6):455-460.

44. Trbovich M. Efficacy of Various Cooling Techniques During Exercise in Persons With Spinal Cord Injury: A Pilot Crossover Intervention Study. *Top Spinal Cord Inj Rehabil.* 2019;25(1):74-82.

45. Webborn N, Price MJ, Castle PC, Goosey-Tolfrey VL. Effects of two cooling strategies on thermoregulatory responses of tetraplegic athletes during repeated intermittent exercise in the heat. *J. Appl. Physiol.* 2005;98(6):2101-2107.

46. Bongers CC, Eijsvogels TM, van Nes IJ, Hopman MT, Thijssen DH. Effects of Cooling During Exercise on Thermoregulatory Responses of Men With Paraplegia. *Phys. Ther.* 2016;96(5):650-658.

47. Takashima A, Sato K, Takizawa K, Suzurikawa J, Higuchi Y, Huang M, Teshima Y, Tamura T, Kurabayashi D, Inoue T, Ogata T. Construction of a soft wearable body cooling system for persons with spinal cord injury. *Annu Int Conf IEEE Eng Med Biol Soc.* 2017;2017:913-916.

48. Suzurikawa J, Fujimoto S, Mikami K, Jonai H, Inoue T. Thermophysiological responses induced by a body heat removal system with Peltier devices in a hot environment. *Annu Int Conf IEEE Eng Med Biol Soc.* 2013;2013:6377-6380.

49. Trbovich M, Koek W, Ortega C. Efficacy of water spray for evaporative cooling in athletes with spinal cord injury. *Spinal Cord Ser Cases.* 2019;5:51.

50. Handrakis JP, Ni Guan Z, Nulty JW, Tascione O, Rosado-Rivera D, White D, Bang C, Spungen AM, Bauman WA. Effect of Heat Exposure on Cognition in Persons with Tetraplegia. *J. Neurotrauma.* 2017;34(24):3372-3380.

51. Kumar NS, Bart J, Barton C, Graham ML, Leung PP, Tittley TD, Lee I, Bang C, Bauman WA, Handrakis JP. Core Temperature Lability Predicts the Degree of Sympathetic Interruption and Cognitive Performance during Heat Exposure in Persons with Higher Spinal Cord Injuries. *J. Neurotrauma.* 2021.

52. Cracowski JL, Minson CT, Salvat-Melis M, Halliwill JR. Methodological issues in the assessment of skin microvascular endothelial function in humans. *Trends Pharmacol. Sci.* 2006;27(9):503-508.

53. Roustit M, Cracowski JL. Non-invasive assessment of skin microvascular function in humans: an insight into methods. *Microcirculation.* 2012;19(1):47-64.

54. Notley SR, Meade RD, Kenny GP. Time following ingestion does not influence the validity of telemetry pill measurements of core temperature during exercise-heat stress: The journal Temperature toolbox. *Temperature.* 2021;8(1):12-20.

55. Johnson JM, Minson CT, Kellogg DL, Jr. Cutaneous vasodilator and vasoconstrictor mechanisms in temperature regulation. *Compr Physiol.* 2014;4(1):33-89.

56. Zhang H, Huizenga C, Arens E, Wang D. Thermal sensation and comfort in transient non-uniform thermal environments. *Eur. J. Appl. Physiol.* 2004;92(6):728-733.

57. Mitchell UH, Burton S, Gordon C, Mack GW. The Effect of Being Aerobically Active vs. Inactive on Cutaneous Vascular Conductance during Local Heat Stress in an Older Population. *Front. Physiol.* 2017;8:859.

58. Swift B, McGinn R, Gagnon D, Crandall CG, Kenny GP. Adenosine receptor inhibition attenuates the decrease in cutaneous vascular conductance during whole-body cooling from hyperthermia. *Exp. Physiol.* 2014;99(1):196-204.

59. Sund-Levander M, Forsberg C, Wahren LK. Normal oral, rectal, tympanic and axillary body temperature in adult men and women: a systematic literature review. *Scand. J. Caring Sci.* 2002;16(2):122-128.

60. Marui S, Misawa A, Tanaka Y, Nagashima K. Assessment of axillary temperature for the evaluation of normal body temperature of healthy young adults at rest in a thermoneutral environment. *J. Physiol. Anthropol.* 2017;36(1):18.

61. Tipton MJ, Mekjavic IB, Golden FSC. Hypothermia. In: Bove AA, ed. *Bove and Davis' Diving Medicine* Fourth Edition ed: W.B. Saunders; 2004:261-273.

62. Liang H, Sang Z, Wu Y, Zhang Y, Zhao R. High precision temperature control performance of a PID neural network-controlled heater under complex outdoor conditions. *Applied Thermal Engineering.* 2021;195.

63. Luo S, Androwis G, Adamovich S, Su H, Nunez E, Zhou X. Reinforcement Learning and Control of a Lower Extremity Exoskeleton for Squat Assistance. *Front Robot AI.* 2021;8:702845.

64. National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. In: Center NSCIS, ed. Birmingham, AL: University of Alabama at Birmingham; 2022.

65. French DD, Campbell RR, Sabharwal S, Nelson AL, Palacios PA, Gavin-Dreschnack D. Health care costs for patients with chronic spinal cord injury in the Veterans Health Administration. *J. Spinal Cord Med.* 2007;30(5):477-481.