Title: Exercise in Burn Survivors: Cooling Modalities

NCT Number: NCT04512976

Document Date: May 20, 2024

Form A

IRB # 30204	STU-2020-0334

PROTOCOL FORM / RESEARCH DESCRIPTION

If an item does not apply to your research project, indicate that the question is "**not applicable**" – do not leave sections blank

Click once on the highlighted entry in each box to provide your response. Click the item number/letter or word, if hyperlinked, for detailed instructions for that question. If your response requires inserting a table, picture, etc, you may need to first delete the box that surrounds the answer and then insert your table or other special document.

1. Purpose and objectives. *List the purpose and objectives:*

The purpose of this project is to identify modalities to attenuate excessive elevations in skin and internal body temperatures during physical activity in well-healed burn survivors.

2. Background.

- Describe past experimental and/or clinical findings leading to the formulation of your study.
- For research involving investigational drugs, describe the previously conducted animal and human studies.
- For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol.
- Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference.

You may reference sponsor's full protocol or grant application (section number and/or title) or if none, ensure background includes references.

Please respond to all components of this item, or clearly indicate which components are not applicable.

a. Background

Within the United States hundreds of thousands of severely injured burn survivors are presently enduring the long-term consequences of their injuries. For example, 3-10 years following a severe burn injury fatigue is an "almost universal complaint" and a major barrier in returning to work and performing activities of daily living. Notably, we identified that ~75% of well-healed burned survivors have an aerobic capacity in the lowest 20th percentile relative to age- and sex-matched normative values; values associated with a 3 to 5 fold greater mortality risk [9]. Consistent with these values, well-healed burn survivors have greater all-cause mortality rates, greater hospitalization days for "circulatory diseases", and suffer from greater incidences of ischemic heart disease, heart failure, diabetes, and cerebrovascular disease (including stroke) relative to matched non-burned cohorts. Though the mechanisms responsible for these consequences are unknown, similar adverse responses are observed in sedentary non-burned individuals. Given our findings that burn survivors are capable of realizing the positive cardiovascular and metabolic benefits of physical activity (given sufficient encouragement), a critical unanswered question is, "why do burn survivors (as a population) not participate in physical activity sufficient to maintain optimal health and to avoid the negative sequelae associated with a sedentary lifestyle?"

Burn survivors have severely impaired body temperature regulation, owing to permanent impairments in the primary thermoeffectors necessary to dissipate heat, namely profoundly blunted skin blood flow and sweating responses in the injured skin. Given that excessive elevations in skin and internal body temperatures impair perceptual, behavioral, and performance aspects of physical activity, we propose that this heat intolerance is an impediment to an active lifestyle in burn survivors. Thus, identifying effective modalities to attenuate the excessive elevations in skin and internal temperatures during physical activity in burn survivors will aid in their full rehabilitation by removing a substantial barrier (e.g., heat intolerance) to participating in such activities. To that end, a primary objective of the proposed work is to identify cooling modalities that are effective in burn survivors, thereby helping

these individuals enjoy the rehabilitative and health benefits of physical activity and curtail adverse consequences of a sedentary lifestyle.

b. Current practice

N/A

3. Study Design.
Describe the study design (e.g., single/double blind, parallel, crossover, etc.) Consider inserting a scheme to visually present the study design.

We will conduct a randomized crossover design study. Non-burned control subjects, subjects who experienced burns covering ~20% to 40% of their body surface area, and subjects having burns >40% of their body surface area will be investigated. In one of the three environmental conditions outlined in Table 1, subjects will exercise while receiving one of the indicated cooling modalities.

Table 1: Proposed environmental conditions and cooling modalities.

Environmental Conditions	Condition A	Condition B	Condition C	Condition D
24 °C; 40% RH	Control (no fan or skin wetting)	Skin wetting only	Fan only	Skin wetting with a fan
30 °C; 40% RH	Control (no fan or skin wetting)	Skin wetting only	Fan only	Skin wetting with a fan
No higher than 40 °C; 40% RH	Control (no fan or skin wetting)	Skin wetting only	Fan only	Skin wetting with a fan

Table 2: Procedures and visits

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Informed Consent	X				
Urine Sample	X	X	X	X	X
Body Composition (DXA)	X				
Exercise Test	X				
12 lead ECG	X				
Alcohol Intake Survey	X				
International Physical Activity Survey	X				
Screening Questionnaire	X				
Heart Rate	X	X	X	X	X
Blood Pressure	X	X	X	X	X
Internal Temperature		X	X	X	X
Skin Temperature (including infrared imaging)		X	X	X	X
Skin blood flow and sweating measures		X	X	X	X
Blood samples		X	X	X	X

Metabolic Rate & ventilation		X	X	X	X
Perceptual Survey		X	X	X	X
Echocardiogram	**X**	X	X	X	X

4. Research Plan / Description of the Research Methods:

4.a. Provide a **comprehensive narrative** describing the **research methods**.

1) Provide the **order in which tests/procedures will be performed**,
2) Provide the **setting** for these events and a description of the **methods used to protect privacy** during the study.
3) Provide the **plan for data analysis** (include as applicable the **sample size calculation)**

Please respond to all components of this item, or clearly indicate which components are not applicable.

The setting for all visits will be the Institute for Exercise and Environmental Medicine. Subjects will be recruited from: 1) the UTSW or IEEM volunteer research registry, 2) flyers/advertisements posted/shared at major burn centers throughout the United States, 3) info-articles and email blasts disseminated by our collaborator, the Phoenix Society, which is the largest burn support group in North America, as well as smaller (i.e., regional) burn support groups, 4) database of burned soldiers via our collaboration with the US Army, and 5) database of burn survivors maintained at UT Southwestern by the Co-Investigator (Karen Kowalske, MD) IRB protocol number: Study00000105. The latter database will be accessed by the Study Team to identify burn survivors who meet the inclusion/exclusion criteria outlined in Form C. Those individuals will be informed of the study, along with instructions to contact the Study Team should they be interested in participating.

Trials will be conducted in controlled laboratory settings. Burn survivors and non-burned individuals will perform bouts of exercise at a given environmental temperature as outlined in Table 1. Subjects will be required to perform exercise across all four of the conditions (i.e., Conditions A-D in Table 1) for a given environmental temperature. However, a subject will not be required to perform the battery of trials across all three environmental temperatures. Within a particular environmental temperature, the order of exposure for Conditions A-D will be randomized. Prior to being assigned to an order of cooling modalities for any given environmental temperature, we will obtain participant demographics, anthropometrics (body mass, height and composition) and aerobic capacity data.

For a particular environmental chamber trial, baseline data will be collected while resting in a thermoneutral environment outside of the environmental chamber. Participants will then enter the environmental chamber and be seated while instrumentation is completed. Subjects will then exercise at a mild/moderate workload for 60 min. The assigned cooling modality will be employed throughout the exercise bout. The primary assessed variables are the increase in internal and skin temperatures. Upon completion of the exercise bout, participants will rest for no more than 60 minutes in the chamber during which time we will monitor temperatures and obtain echocardiogram images, then the environmental temperature will be reduced and subjects will be de-instrumented.

Data will be digitized upon acquisition, name encrypted, and stored in password protected computer folders. Only approved personnel will have access to subject files that will otherwise be locked. Research data and medical history will be available to the PI and his staff. Members and staff of the Institutional Review Board (IRB) at UT Southwestern Medical Center and Texas Health Presbyterian Hospital may review subjects' records. A representative of these IRBs may contact the subject for information about their experience with this research project. The subject may refuse to answer any questions the representative of the IRB may ask. All subjects' information will be kept confidential unless the subject

gives the researchers permission to share with others or if the investigators are required by law to release it. All hard copy documents will be stored behind at least two locked doors/devices and only individuals who are involved in this research project can access the files. Information contained in reports or publications issued as a result of this research project will be presented in such a way that the subject identity will not be revealed. The signed consent form will be kept on file in the subject's laboratory chart. Disclosure of information to third parties will be prohibited.

Statistical support will be provided by Linda Hynan, Ph.D., Professor in the Department of Clinical Sciences, Division of Biostatistics at UT Southwestern Medical Center at Dallas. Descriptive statistics (i.e., group characteristics such as age, body mass, BSA burned, physical activity questionnaire data, etc.) will be analyzed via one-way analysis of variance to compare the three study groups. Within each environmental exposure, the primary evaluation will address an expected interactive effect of group and the employed cooling condition (e.g., Conditions A-D as outlined in Table 1) on the magnitude of the elevation in internal body temperature to 60 min of exercise. These data will be statistically analyzed via a two-factor mixed-effects model repeated measures analysis with main factors of group and the applied cooling condition (crossover repeated factor), and their interaction, with subject modeled as a random effect and specifying covariance structure, using SAS Proc Mixed. Potential mechanisms contributing to differing elevations in internal body temperature (e.g., differences in magnitude of changes in skin temperature and skin surface water vapor pressure) as a result of the exercise bouts will be statistically evaluated via the same approach. The extent and significance of the expected interactions will be statistically explored post-hoc with appropriate comparisons derived from the models' least square means contrasts, applying Bonferroni type adjustments for multiple testing.

We estimated power to detect a 0.5 °C mean difference in the elevation in internal body temperature to the exercise bout between groups. This number was obtained from one of our prior studies in which similar thermoregulatory responses to exercise in burn survivors were assessed, with a standard deviation of the elevation in internal body temperature being ~0.3 °C. Based upon these estimates, 12 subjects per group for each environmental exposure would provide omnibus power of 0.94 for group differences in the elevation in internal body temperature of 0.45 °C at an alpha of 0.05 and power of 0.84, using an adjusted alpha of 0.0125 to account for multiple comparison evaluations of the four interventions between groups. For the within group comparison, power is >0.9 to detect a difference in the increase in internal body temperature of 0.4 °C at an alpha of 0.0125 (power analyses from: NCSS PASS 15). Nevertheless, we will enroll 18 subjects per group (9 male and 9 female) for each environmental exposure to allow for attrition as well as provide additional power to evaluate any sex-related differences, should they become apparent. Randomization within groups for the order of the applied cooling modality will be implemented with a Latin square blocking design.

4.b. List of the study intervention(s) being tested or evaluated under this protocol

☐ **N/A -** this study does not test or evaluate an intervention. Skip to item 4.d.

#	Study intervention(s) being tested or evaluated under the protocol *Add or delete rows as needed*	Affiliate Place a check next to institution(s) where the intervention will be performed	Local Standard Practice? Indicate whether the intervention is considered acceptable practice locally for applicable institutions
1	Skin cooling (fan and skin wetting)	☐ UTSW	☐ Yes
		☐ PHHS	☐ Yes
		☐CMC	☐ Yes
		☒THR	☐ Yes
		☐TSRH	☐ Yes
		☐ Other: _____	☐ Yes

4.c. Risk:Benefit Analysis of study interventions being tested or evaluated under this protocol

For each study intervention identified in section 6b above, complete a risk:benefit analysis table.

(Two tables are provided, copy & paste additional tables as needed or delete both tables if this study does not test an intervention)

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4.c.
Study Intervention #1
Cooling Modalities (fan and skin wetting)

List each group exposed to this intervention on a separate line. (e.g., experimental, control, Arm A, Arm B, etc) **Or** state All Groups/Subjects	For each group, list the **benefits** of this intervention. (Benefits can be directly from the intervention or from a monitoring procedure likely to contribute to the subject's well being). If there are no benefits, state "none".
All Groups/Subjects	None; the research subjects will not directly benefit from the cooling modality interventions.

If you are requesting a Waiver of Informed Consent, complete the table below.

If you have a consent form, **list the reasonably foreseeable risks in the consent form (and do not complete this section).**

List the risks according to the probability (likely, less likely or rare) and magnitude (serious or not serious).
(include: 1) expected adverse events; 2) rare and serious adverse events; 3) all other psychological, social, legal harms)
Do not delete frequency. Frequency must be estimated because it will assist you with determining which adverse events will require prompt reporting.

	Not serious	**Serious**
Likely These risks are expected to occur in more than **20** out of **100** subjects.	•	•
	Not serious	**Serious**
Less likely These risks are expected to occur in **5-20** subjects or less out of **100** subjects.	•	•
		Serious
Rare These risks are expected to occur in less than **5** subjects out of **100**		•

4.d. List ALL other research procedures or components not listed in table 4.b.
The combination of Tables 4b and 4d should account for all of the research procedures that will take place during this study.

Consider grouping similar procedures under a single component (e.g., blood work, CT = safety assessments)

#	Research component • **individual procedures** *example:* **Eligibility Assessments** • History and physical • Questionnaire • Laboratory tests *Add or delete rows as needed*	**Column A** **Local Standard Practice** Indicate the number of times each procedure will be performed as stipulated in the research plan **that would be performed if the participant were not participating in the study.**	**Column B** **Research Only** Indicate the number of times each procedure will be performed solely for research purposes *(meaning that the participant would not undergo the same number of procedures or would not undergo the procedure(s) at the same frequency if they were not participating in the study)*	**Column D** **Risks** **If you are requesting a Waiver of Informed Consent, complete the table below.** List the reasonably expected risks for each procedure or group of procedures under the following categories as appropriate: • Serious and likely; • Serious and less likely; • Serious and rare; • Not serious and likely; • Not serious and less likely
1	**Screening Assessment**			
	Urine Sample	0	1 sample for this screening	
	Body Height	0	1	
	Body Mass	0	1 sample for this screening	
	Blood Pressure	0	Up to 6 for this screening	
	12-lead Electrocardiogram	0	1	
	Body Composition via DXA	0	1	
	Graded Exercise Test	0	1	
2	**Exercise Measurements**			
	Environmental Conditions	0	Continuously	
	Heart rate via ECG	0	Continuously	
	Urine Sample	0	1 sample per visit	
	Body Mass	0	Up to 4 samples per visit	
	Blood Pressure	0	Up to 20 samples per visit	
	Internal temperature (temperature sensor pill)	0	Continuously	
	Internal temperature (via rectal thermometer)	0	Continuously	
	Internal Temperature (suppository pill)	0	Continuously	
	Skin temperature/humidity	0	Continuously	
	Skin temperature (infrared imaging)	0	Up to 6 per visit	
	Local sweat rate	0	Continuously	
	Activated sweat gland	0	Up to 6 per visit	
	Skin blood flow	0	Continuously	
	Peripheral intravenous catheter and blood samples	0	Up to 4 per visit	
	Cardiac output (gas rebreathing)	0	Up to 6 per visit	
	Metabolic rate and ventilation	0	Up to 8 per visit	
	Perceptual Questionnaires	0	Up to 20 per heat-wave simulation	
	Echocardiogram	0	1 sample per visit	

5. Safety Precautions. *(Describe safeguards to address the serious risks listed above.)*

a. Describe the procedures for protecting against or minimizing any potential risks for each of the more than minimal risk research procedures listed above.

Exercise in the prescribed climate conditions: Internal body temperature will be monitored throughout each experiment. The protocol will stop, and the environmental temperature will be reduced, in the unlikely occurrence that internal body temperature exceeds 39.5°C or upon any indication of adverse cardiovascular or neurological symptoms (e.g., lightheadedness, hypotension, hypertension, nausea, etc. Our experiences are that the burn survivors and non-burned control subjects tolerate the exercise bout well. Upon completion of each protocol, we will ensure that each subject is normothermic and adequately hydrated prior to being permitted to leave the laboratory.

Peripheral intravenous catheter and blood samples: There is a small risk of infection and a still smaller risk of a blood clot or breakage of the catheter. The likelihood of these complications is remote (less than 1 in 10,000) when the procedure is carried out by trained personnel and proper equipment is used, as during this study. There is also a small risk of the catheter perforating the vein or not being inserted into a blood vessel. The participant may have discomfort, bleeding, and/or bruising and on rare occasions, a person may feel dizzy or faint.

Body composition (DXA): The radiation exposure from this procedure is negligible and is estimated to be 0.06 mR, which is equivalent to 1/286th the dose of a standard chest x-ray and less than a day's exposure to natural radiation.

Sweat gland activation with iodine embedded paper: This procedure will not be performed if a participant has a known allergy to iodine. Given the very small amount of iodine embedded in the paper, even if the participant is unknowingly allergic to iodine, this exposure is unlikely to cause any irritation; an exception could be a minor rash if the person is particularly sensitive.

Graded Exercise Test: During exercise stress tests, the risk of having a "heart attack" or even dying goes up slightly (less than 1/100,000 tests) relative to moderate intensity exercise. There are no additional risks involved with completing the graded exercise test beyond that associated with exercise and hard physical exertion. Every precaution will be taken to minimize the risk by closely monitoring vital signs (blood pressure, heart rate and rhythm) throughout the exercise. These tests will be stopped if signs or symptoms of cardiac ischemia develop, if excessive hypertension or hypotension develop, or if arrhythmias occur during exercise. American College of Sports Medicine guidelines will be followed regarding physician attendance for graded exercise tests. Additionally, a research nurse will be present during the graded exercise test to interpret any danger signs and symptoms.

Internal temperature (temperature sensor pill): See comments above regarding the internal body temperature cut-off (39.5 °C) for all trials. This pill should not be taken if the subject weighs less than 80 pounds, nor should the subject take this pill if they have or have had any gastrointestinal disease or surgery. The research nurse will also check each subject's medical history prior to the pill being swallowed. Should a subject have any contraindications in taking the pill, the pill will not be ingested. Rather, rectal temperature will be obtained.

Internal temperature (rectal thermometer): If rectal temperature is used, the subject will self-insert a small single-use rectal temperature thermometer to a pre-marked depth of 15 cm. The rectal thermocouple will not be inserted if they have or previously had inflammatory bowel or colon disease and/or rectal or anal surgery. They also may not use the thermometer if they currently have hemorrhoids (internal or external), rectal bleeding, diarrhea or fecal impaction in the rectum. Each

subject's medical history will be verified prior to self-insertion of the rectal thermometer by the research nurse.

Internal temperature (suppository pill): If a suppository temperature sensing pill is used, with a gloved hand the subject will self-insert a lubricated temperature sensor pill (like a suppository) into their rectum. This pill will be discharged through normal defecation. This temperature sensing pill will not be used if the subject currently has hemorrhoids (internal or external), rectal bleeding, diarrhea or fecal impaction in the rectum. Each subject's medical history will be verified by the research nurse prior to self-insertion of this pill.

b. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects.

A research nurse will continually monitor the well-being of each subject. In addition, physicians and nurses at the Institute for Exercise and Environmental Medicine will assist as needed. All members of the research team are (at a minimum) Basic Life Support certified and have successfully completed at least two 'mock' codes per year. All experiments will take place in a hospital environment with a crash cart (inclusive of cardiovascular medications and a defibrillator) located within 100 feet of the laboratory.

Though unlikely, should a subject experience signs or symptoms of a possible or ensuing adverse event (e.g., hypotension, light headedness, nausea, significant discomfort, etc.) during a particular procedure, that procedure will be stopped and the environmental chamber will be cooled. The subject will remain in the laboratory until they have fully recovered. Upon screening, participants will be given contact information for both a nurse and the principal investigator to contact in case any adverse event occurs following discharge from experimental days.

c. Will the safeguards be different between/among groups?

☐ Yes ☑ No

If yes, describe here