Effect of a Novel Cooling Device on Brain Temperature

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September 29, 2021

Human Subjects Research Protocol

PROTOCOL SUMMARY

Project Title: Effect of a Novel Cooling Device on Brain Temperature

Protocol Version Date: September 29, 2021

Principal Investigator: Adam S. Sprouse Blum, MD

Check the type of the review:

[x] Full convened meeting - The IRBs employ the convened meeting review process for review and approval of studies that are more than minimal risk.

[ ] Expedited review - The IRBs employ the expedited review process for approval of studies that are determined to be minimal risk and only involves activities such as; prospective collection of biological specimens for research purposes by noninvasive means (blood collection, salvia, nail clippings), collection of data through noninvasive procedures (ultrasounds, MRI, physical sensors) and research on behavior such as perception, cognition, motivation, identity, language and communication.

PURPOSE AND OBJECTIVES

Purpose: The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.

Background information, including literature review

Brain cooling is the most potent neuro-protectant known.[1] Its mechanisms include decreasing metabolic activity,[2] inhibiting the release of harmful neurochemicals, and maintaining the blood brain barrier.[3] In animal studies, brain cooling consistently improves neurologic outcomes across a variety of species[4-8] and across a wide range of disorders including ischemic stroke,[9] subarachnoid hemorrhage,[10] traumatic brain injury,[11] seizures,[12] and cerebral edema.[13] In humans, brain cooling has consistently demonstrated benefit and is the standard of care after cardiac arrest[14] and in ischemic encephalopathy.[15] However, attempts to translate the beneficial effects of brain cooling from animals to humans in other neurologic conditions, such as ischemic stroke,[9] traumatic brain injury,[16] and epilepsy,[12] have demonstrated mixed results. This variability may be partially explained by differences in animal and human physiology. However, a more likely explanation is that we are cooling animal and human brains differently.

The first key difference between animal and human brain cooling studies is with animals the brain can be cooled selectively, without affecting the temperature of the rest of the body, by infusing cold fluids into or around the brain (e.g. via the carotid artery,[4] subdural space,[6] or nasal cavity[5]). In humans, these invasive methods are impractical and a different approach has been taken, whole body cooling. Whole body cooling is typically achieved either by running cold saline through a person's veins or covering the entire body with surface cooling pads (e.g. Arctic Sun™). While this approach is effective at lowering brain temperature, it comes at a cost. Whole body cooling has been associated with negative iatrogenic effects including increased blood pressure, altered coagulation, and increased risk of pneumonia and sepsis.[17, 18] Whole body cooling also requires sedation to be tolerated, restricting its use to an intensive care setting. The second key difference between animal and human brain cooling studies is timing. In animal studies, neurologic trauma is induced. Therefore, cooling can be implemented immediately after injury. In humans, there is a mean delay of 160 minutes from the time emergency personnel revive a patient to the initiation of in-hospital cooling.[19, 20] As time passes, irreversible pathophysiologic changes accumulate in the brain.[17, 21] Early cooling has been shown to be superior to delayed cooling in both animals[22] and humans.[20, 23] What is needed is a device that selectively cools the brain without affecting the temperature of the rest of the body that can be applied close to the time of injury without sedation.

Prior attempts have been made to selectively cool the brains of non-sedated patients with variable success. In two studies,[24, 25] ice packs were applied to the necks of healthy subjects for 15 and 40 minutes, respectively. Brain temperature decreased by as much as -0.7 °*C*. These studies were limited by an inadequate method of cooling (*i.e.* static ice packs) and short duration of treatment. In a separate pair of studies, intranasal cooling was achieved by circulating cold saline through a pair of nasal catheters or by spraying a coolant-gas mixture toward the roof of the nasopharynx, both for 60 minutes. Brain temperature decreased by -1.8 °*C* and -1.4 °*C*, respectively.[26-28] Adverse events included the development of small ulcers in the nasal cavity in 3 of 10 subjects in the first (circulated saline) study, with 6 of 10 subjects finding the catheters unpleasant.[28] In the second (coolant-gas mixture) study, subsequent testing raised concerns about increases in systolic blood pressure[29] and an adverse event was reported in which the nasal catheters tracked through the superior nasal meatus causing air bubbles to track through the cribriform plate, tearing the dura, and allowing gas bubbles to enter the brain.[30]

Research rationale and objectives

We propose a novel method to cool the brain selectively, with minimal anticipated impact on the temperature of the rest of the body, by adapting the Arctic Sun to cool the neck. The skull is an effective insulator, making the brain resistant to changes in temperature from externally applied sources.[1, 31, 32] The neck, however, lacks these insulating properties and poses a logical

location to attempt to intervene on brain temperature. Long-distance runners in heat exhaustion cool the body by applying ice packs to the groin and axilla, locations where large blood vessels come close to the skin surface. The same technique could be applied to the neck. The carotid and vertebral arteries (Figure) come close to the skin surface for 14-22 cm (5.5-8.7 in)[33] along the anterior neck and supply 100% of the brain's blood supply. If we can sufficiently cool the deep tissues of the neck around the carotid and vertebral arteries, we may be able to cool the blood passing through them to cool the brain.

The objective of this study is to measure core brain temperature using MR thermometry during active neck cooling with the Arctic Sun. MR thermometry is a non-invasive MRI technique to measure brain temperature with an accuracy of ±0.2 °C,[34-36] and has been previously used at our institution.[25] Neck cooling will be achieved by connecting the Arctic Sun to Bard's existing small universal pad (product code 318-01-04) which has an active surface area of 30.5 cm (12 in) length x 14.5 cm (5.7 in) height. An MR technologist will help the subject apply the wrap to the front of the neck, over the carotid and vertebral arteries, before lying down in the MR scanner. A 25-foot insulated tubing set will be required to keep the Arctic Sun device outside of the MR suite in the control room. The neck wrap itself does not contain metal and is MR compatible. The Arctic Sun will be operated in manual mode such that subjects will be able to adjust the temperature of the circulated water by communicating with the study coordinator using a 2-way intercom system. The water temperature will be adjusted until the subject identifies the lowest tolerable temperature. Vital signs, tympanic membrane (ear drum) temperature, and skin temperature will be measured throughout the study. Tympanic membrane temperature will be measured using a fiber optic thermometer secured in one of the subject's ear plugs. Tympanic membrane temperature has previously been used as a surrogate marker for brain temperature, though has limitations.[37] Skin temperature will be measured using a fiber optic, applied to the skin under the neck wrap. While prior studies suggest a 1 °C decrease in brain temperature can be achieved non-invasively within 60 minutes,[38] we plan to cool subjects for ~120 minutes given that this is a novel method of cooling. Brain temperature will be measured in one-minute intervals throughout the study. After the first three subjects complete the study, patient tolerability and the temperature trend (*i.e.* has brain temperature reached plateau?) will be assessed. Based on these factors, consideration will be given to lengthening the duration of the intervention for the remaining subjects. All subjects will complete the intervention twice, once cold and once at body temperature. The body temperature intervention will serve as a control to confirm that any change in brain temperature measured in the cooling arm is due to the temperature of the circulated water.

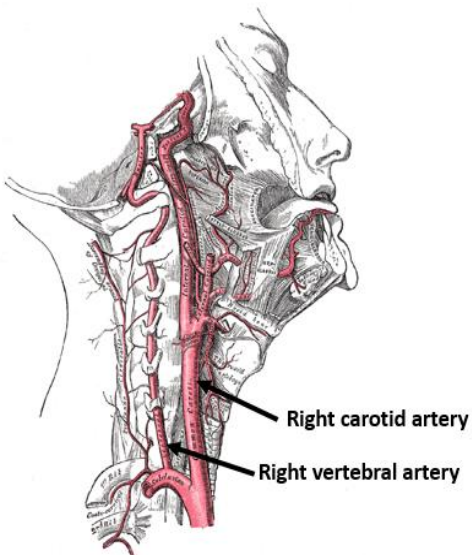

Figure. *Right carotid and vertebral arteries. Adapted from the 20th U.S. edition of Gray's Anatomy of the Human Body.*

If the brain can be cooled using this novel method, there are current and future indications in which this technique could be applied. For example: 1. <u>In the ICU:</u> Since neck cooling is not anticipated to significantly impact body temperature, adding the neck wrap to the standard Arctic Sun body cooling regimen may permit the same depth of brain cooling without cooling the body as deeply. If the body does not need to be cooled as deeply this may be associated with downstream benefits including fewer iatrogenic adverse effects observed with whole body cooling; 2. <u>In the ambulance:</u> Since neck cooling does not require sedation to be tolerated this opens the door to settings outside of the ICU and brings cooling to the patient rather than the patient to the cooling, thereby narrowing the gap between the neurologic event and the initiation of brain cooling. The Arctic Sun has been rarely used in an ambulance setting. However, if sedation is not needed, this may make the use of the Arctic Sun in an ambulance setting more feasible. When the patient arrives at the hospital and is admitted to the ICU they could then be sedated and transitioned to whole body cooling; 3. <u>In an outpatient setting:</u> It is also conceivable in the future that a smaller, more portable Arctic Sun device could be devised. This would allow for the application of brain cooling in a variety of non-critical neurologic conditions such as after sports related concussions on the field or for migraine.

References. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.

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Objectives: Clearly state the primary and secondary objective(s) of the study.

The primary objective is to describe change in brain temperature with application of neck cooling.
The secondary objective is to describe how anthropomorphic characteristics affect the change in brain temperature.

METHODS AND PROCEDURES

Study Design: Describe the research design, including a description of any new methodology and its advantage over existing methodologies.

This is a randomized paired cross-over study in which each subject will undergo MR thermometry with and without active cooling to assess the effect of surface neck cooling on brain temperature.

Procedures: Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc.

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Once a subject has been consented, they will schedule a visit at the UVM MRI Center for Biomedical Imaging. The study coordinator will contact the subject 24-48 hours prior to the scheduled visit to complete a COVID-19 Assessment to confirm eligibility to come to campus. After safety to come to campus is confirmed, the study coordinator will meet the subject at an agreed upon location at the UVM Medical Center (*e.g.* the lobby of the MRI Research Center). Once at the MRI Research Center they will review the MRI Safety Questionnaire and ask whether any changes have occurred since it was completed. All questions will be answered before proceeding.

When the subject has no further questions, the study coordinator will measure the subject's height, weight, and neck circumference. Next, the MR technologist will review the MRI Safety Questionnaire then escort the subject into the MRI suite and help them lie on the MRI scanner bed. Once on the scanner bed the MR technologist will apply the adhesive wrap to the subject's neck (Bard product code 318-01-04). Two fiber optic thermometers will be used to measure surface temperature. One will be embedded in an ear plug which will be gently inserted into one of the subject's ears in order to measure tympanic membrane (ear drum) temperature. The other will be placed under the neck wrap between the wrap and the surface of the skin in order to measure the subject's neck skin temperature. Both the neck wrap and the fiber optic thermometers are MRI compatible. In order to keep the Artic Sun cooling device outside the MRI suite, a 25-foot insulated tubing set, which does not contain metal, will be used. The tubing will go from the Arctic Sun cooling device in the control room, through a wave guide in the wall between the control room and the MRI suite, to the wrap on the subject's neck. A similar cooling set up has been used previously by the same investigators at our institution.

A standard MRI compatible set up will be used to measure the subject's vital signs, including heart rate and blood pressure at 15-minute intervals throughout the study. A modified bedside shivering assessment will be completed by the study coordinator every 30 minutes and a blanket will be offered to the subject if mild shivering is detected, or if the subject requests it. 60 minutes into the intervention the MR technologist will conduct a "skin check," examining the subject's skin under the wrap.

The subject will stay in constant communication with the MR technologist and study coordinator using a 2-way intercom system throughout the study. As an additional safety measure, the subject will also have a squeeze ball in their hand which sets off an alarm in the control room.

At this point, the subject will be ready to undergo their first intervention.

The subject will then be randomized to either the cold or body-temperature study arm using a sealed envelope system. The subject will be informed which arm of the study they were randomized to.

The intervention will start when the subject indicates they are ready to begin. At the beginning and end of each intervention, an MRI technique called pCASL will be used to quantify blood flow to the brain. MR thermometry will be used throughout the two hour intervention to measure core brain temperature every ~1 minute. The Arctic Sun will be operated in manual mode. By operating in manual mode, the study coordinator can set the temperature of the circulating water on the device touch screen. Regardless of which study arm the subject is in, the water temperature will be started at body-temperature (37°C).

Note: The Arctic Sun device will be operated by the study coordinator for the duration of the study. Bard will provide training on how to operate the device prior to enrollment and will be available for technical support should it be needed.

In the **body-temperature** arm, the water temperature will be left at 37°C for the duration of the study.

In the **cold arm**, over ~5-10 minutes, the study coordinator and the subject will lower the temperature of the circulating water to find the lowest tolerable temperature. The circulating water will be kept at this temperature for the remainder of the 2-hour intervention unless the subject indicates they would like to adjust the temperature of the circulating water (either up or down). The subject can adjust the temperature of the circulating water as many times as desired during the intervention. The subject's skin temperature will be constantly monitored, and recorded, using the fiber optic thermometer discussed earlier, and will never be allowed to drop below 6°C. This lower limit for skin temperature was selected based on the fact that lower skin temperatures are associated with a phenomenon known as the Hunting reaction, a protective but painful response of the skin in which vasodilation and vasoconstriction occur (Daanen H. Finger cold-induced vasodilation: a review. European journal of applied physiology. 2003; 89(5):411-426).

At the conclusion of each intervention, the subject will complete a 5-minute questionnaire about their experience including open-ended questioning to identify any adverse effects experienced.

A second intervention will be scheduled, ideally within the following 7 days.

The study coordinator will complete a COVID-19 Assessment 24-48 hours prior to their second visit to confirm eligibility to come to campus.

The second intervention will be identical to the first. If the subject was randomized to the cold intervention for their first visit they will cross over to the body temperature intervention for their second visit, and vice-versa.

The purpose of the body temperature intervention is to serve as a control for our cooling intervention in order to be certain that any change in brain temperature observed during the cooling intervention is due to the temperature of the circulating water.

Describe required screening procedures performed before enrollment and while on study.

When a subject responds to our recruitment materials, the study coordinator will review the Key Information portion of the Consent with the subject via phone or Zoom tele-video. Subjects who remain interested will be screened for study eligibility using an Eligibility Checklist. Eligible subjects will have the full Consent Form reviewed with them during a Zoom tele-video call. Ineligible subjects will be notified of the reasons for ineligibility and what will happen with the eligibility information they have already given using a script (see Eligibility Checklist for script).

Verbal permission to email the eConsent to the subject will be obtained using the following language: "Because UVM can't control the security of email messages once we send them, we need your permission to email you. Do you want to receive the link to the eConsent via email?"

Verbal permission will be documented in REDCap. The eConsent will be reviewed with the subject. The consent process will take approximately 25 minutes. The subject (and the study coordinator) will be able to sign the eConsent electronically. The fully executed consent will be available for the subject to download or, if they prefer, it will be emailed to them. The Consent Process Documentation form will be utilized to document consent.

For research involving survey, questionnaires, etc.: Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation.

☐ **Not applicable**

1. **Eligibility Checklist** *(3 minutes)***:** The study coordinator will use this brief yes/no questionnaire when contacted by an interested subject to confirm study eligibility.
2. **MRI Safety Questionnaire** *(3 minutes)***:** The MRI Safety Questionnaire has been implemented into the Eligibility Checklist to confirm safety to undergo an MRI. This form will be reviewed with the subject at their first and second visits to the MRI Research Center to confirm no changes have occurred since it was completed.
3. **Data Sheet** *(2.5 hours/intervention)***:** The study coordinator will complete the research Data Sheet at each visit. Subject height, weight, and neck circumference will be collected prior to starting the intervention and water temperature, skin temperature, vital signs, and bed side shivering assessment will be collected during the intervention. This data sheet also includes questions for the subject at the end of the intervention about their experience, including open-ended questioning to identify any adverse effects they may have experienced.

TYPES OF PROCEDURES (Please do not use the "other" option unless the procedure is not listed.)

Check all that apply.

☐	Survey (mail, telephone, in-person, on-line)	☐	Blood drawing:	Vol.	☐	Over days, weeks?
☐	Medical exams/history					Type & Amt.

	Deception ***see below**		Surgery		Collection of Urine and/or Feces
	Observation		Drug Administration		HIV Testing
	Photographs	x	Device Use		Ultrasound (e.g. echocardiogram)
	Audio Recording		Exercise		Imaging (e.g. CT scan, DEXA, mammogram, PET scans, SPECT)
	Video Recording		Diet		Use of Radiation treatment
	Interviews in person or by phone		Pathology Specimens (retrospective)		Use of Radioactive substances (e.g. radiolabeled antibodies, drugs or contrasts)
	Focus Groups		Genetic Materials (DNA)** **see below**		MRI (for treatment studies)
	Review of prospective data	x	Questionnaires	x	MRI (not for treatment studies)
	Review of retrospective data		Diaries		Tissue (obtained for clinical purposes)
x	Recording of Identifiable Data		Pregnancy Tests		Tissue (obtained solely for research)
	Electrocardiograms				
	Sensitive Data (criminal or sexual conduct, drug or alcohol conduct or use)	(specify):			

****If genetic information is being collected, GINA language must be added to the consent form.**
*****Deception typically involves withholding information from the potential subject and would require an alteration to the consent process.

Statistical Considerations: Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.

Primary outcome: Change in brain temperature

The analytic goal is to describe the change in brain temperature with application of cooling. Brain temperature is a continuous variable. We will use a difference-of-differences model where each subject contributes changes in brain temperature both with and without active cooling where:

$$\Delta T_k = (T_{CE,k} - T_{CB,k}) - (T_{WE,k} - T_{WB,k})$$

ΔT_k = net change in brain temperature for subject k
$T_{CE,k}$ = ending brain temperature, cold intervention for subject k
$T_{CB,k}$ = beginning brain temperature, cold intervention for subject k
$T_{WE,k}$ = ending brain temperature, warm intervention for subject k
$T_{WB,k}$ = beginning brain temperature, warm intervention for subject k

$$H_0: \sum \Delta T_k \neq 0$$

Assuming a significance level of 0.05, power of 0.90, and standard deviation of 0.8 *°C* (twice the size of previously published values[Ref]), Student t test requires 13 subjects to detect a change of 0.8 *°C*. We plan to enroll 15 subjects to allow for loss to follow-up between the two visits.

Ref: Curran EJ, Wolfson DL, Watts R, Freeman K. Cold Blooded: Evaluating Brain Temperature by MRI During Surface Cooling of Human Subjects. Neurocritical care. 2017;27(2):214-219.

Secondary outcome: Describe how anthropomorphic characteristics affect change in brain temperature

To help us understand how anthropomorphic characteristics affect the change in brain temperature we will measure the height and weight of each subject to the nearest cm using a calibrated stadiometer and to the nearest 0.5 kg using a calibrated clinical scale. Neck circumference will be measured using a tape measure using the standardized methods described by Lohman, *et al.*[Ref] Distance from the skin surface to the carotid artery will be measured by a board certified neuro-radiologist on MRI cross-section as the shortest distance from the wall of the common carotid artery to the skin, measured 2 cm below the carotid bifurcation.
The goal is to describe the relationship of each body characteristic to the change in brain temperature with cooling (ΔT). We will begin by drawing scatter plots of each characteristic against ΔT and then select a model or transformation (linear, quadratic, U-shaped, etc.) to allow a simple regression analysis. Because of the preliminary nature of the study and limited sample size, we do not plan multivariate models or formal hypothesis testing and expect to attain only a rough idea of the relationships in the data. However, these initial observations may supply valuable insights to drive future research.

Ref: Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Vol 177: Human kinetics books Champaign, IL; 1988.

Risks/Benefits: Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.

Risks:

We will minimize physical:

- Risk of skin damage by *excluding* patients with certain medical conditions including Raynaud's disease, pernio (also known as chilblains), and subjects with signs of ulcerations, burns, hives or rash where the neck wrap is applied. We will also *warn* patients who have an increased risk of skin damage due to certain medical conditions including diabetes, peripheral vascular disease, poor nutritional status, steroid use, and history of skin allergies or sensitivities. Another way risk of skin damage will be minimized is by staying in constant communication with the subject using a 2-way intercom system and letting the subject direct the slow drop in temperature of the neck wrap. The subject's skin temperature will also be continuously monitored, and recorded, by the study coordinator using an MRI compatible fiber optic thermometer placed between the neck wrap and the subject's skin. The skin temperature will not be allowed to drop below 6°C. This temperature was chosen in light of the fact lower temperatures applied to the extremities have been shown to induce the Hunting reaction, a protective but painful response of the skin in which vasodilation and vasoconstriction occurs (Daanen H. Finger cold-induced vasodilation: a review. European journal of applied physiology. 2003;89(5):411-426). Lastly, the MR technologist will conduct a "skin check" by examining the skin under the wrap one hour into the intervention.
- Risk of vascular phenomena, including stroke by excluding patients with certain medical conditions including venous or arterial occlusive disease (e.g. carotid stenosis) and cryoprecipitation disorders (e.g. cryoglobulinemia).
- Risk of abnormal heart rate or blood pressure by monitoring and recording the subject's vital signs throughout the study.
- Risk of feeling uncomfortably cold by conducting modified bed-side shivering assessments and offering the subject a blanket if they experience mild shivering or request it.
- Risk of fetal harm by excluding women who report they are pregnant during screening for this study and asking if there is a chance they could be pregnant just prior to each of their MRIs. If there is a chance you are pregnant, we would not proceed with the intervention.
- Risks related to the MRI magnet by keeping all metal outside the MRI suite. This will be accomplished by removing all metal from the cooling device (i.e. neck wrap, connectors, tubing). The only aspect of the cooling device that contains metal is the Arctic Sun water circulator. The Arctic Sun will be kept outside the MRI suite, in the MRI control room, using a 25-foot insulated tubing set passed through the wall connecting the two rooms. A similar set up was previously used by the same investigators at our institution. Additionally, the subject will complete the standard MRI Safety Questionnaire, which will be updated and reviewed by MRI staff immediately prior to each of their MRI scans.
- Risk of psychological distress (e.g. claustrophobia) by excluding subjects who report having claustrophobia during the eligibility screen and informing subjects during the consent process they may withdraw from the scanner and remove the neck wrap at any time by alerting the research team using the 2-way intercom or the squeeze ball.
- Risk related to machine malfunction by taking advantage of the Arctic Sun Temperature Management System's multiple built-in safety redundancies and series of Alarms and Alerts when an unsafe condition is detected, such as low (≤3.5C°) or high (≥42.5°C) water temperature, as well an auto-stop feature when such conditions are detected. **See Chapter 6 in the Arctic Sun Service Manual (attached) for additional information on the Alarm/Alert system and the parameters monitored.**
- Risk of tympanic membrane (ear drum) puncture by the tip of the fiber optic thermometer by securing the thermometer in the ear plug such that the tip of the thermometer does not extend beyond the end of the ear plug, by showing the subject the tip of the ear plug, discussing the risk, and asking them to notify us if they feel any discomfort as the ear plug is gently inserted, and by covering the ear plug (once inserted) with earmuffs.

We will minimize risk of loss of autonomy by following standard procedures for obtaining informed consent. We will begin this process when an interested subject calls to express interest in participating by reviewing the Key Information section of the Consent to clarify why the study is being performed, what would be required of them, and the risks and benefits associated with participation. We will emphasize that subject participation (or lack thereof) has no impact on the medical services they will receive and subjects will be reminded there is no penalty for withdrawing from this study.

We will minimize risk of loss of confidentiality and privacy by having all information collected and handled by research staff trained to deal appropriately with sensitive clinical issues. All study information will be treated as confidential and will be available only to research staff and the study sponsor (Bard Medical Division). All data given to the study sponsor will be de-identified. All paper records will be kept in a locked office at UVM/UVM-MC. Electronic records will be stored behind the UVM/UVM-MC firewall. When contacting participants for follow-up, no identifying information other than the first name of the research assistant will be used when leaving messages or speaking to anyone other than the participant him/herself. No information about participants will be released without their permission or where required by law.

Benefits

There are no direct benefits to the subject. There are benefits to society. Because most currently available devices to cool the brain **also** cool the rest of the body and generally require sedation to be tolerated, they can only be used for select conditions in an intensive care setting, and have negative consequences on other organ systems. The goal of this research is to develop a device that non-invasively, selectively cools the brain and could be used in awake patients with critical and non-critical conditions without cooling the rest of the body.

Risk/Benefit ratio
We believe the risk/benefit ratio favors performing this study as the associated risks are small and reversible, while the potential benefit is large.

Therapeutic Alternatives: List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.

x	**Not Applicable**

Data Safety and Monitoring: The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.

The principal investigator will review the research Data Sheet after each study intervention (*i.e.* cold or body-temperature), paying particular attention to any adverse effects reported, and will be responsible to review and promptly address all unanticipated problems throughout the life of the study.

Define criteria to be used for decision making regarding continuation, modification, or termination of the entire study (not individual participation) (i.e. "stopping rules).

Should a serious adverse event occur, we will suspend operations while reviewing potential modifications.

What will be the frequency of the review? Please note that the frequency of reviews should be commensurate with the risk of the study. At a minimum, a review of the data should be conducted annually at time of continuing review. **Forward copies of the data and safety monitoring reports to the 1) IRB, 2) CRC (if applicable), and/or 3) UVMCC (if applicable).**

	Monthly	x	Annually
	Quarterly	x	Other (e.g. by dosing level, no. of subjects enrolled):
	Bi-annually		After each intervention

Will the sponsor be conducting data monitoring visits for this study?

	Yes	x	No		NA

If yes, how often?

N/A

Adverse Event, Unanticipated Problem (UAP), Reportable New Information (RNI): Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.

The principal investigator will be responsible to review all unanticipated problems (UAPs) and the guidelines established by the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed including prompt reporting to the IRB.

Withdrawal Procedures: Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).

Subjects may discontinue their participation in the study at any time. However, data that has already been collected until that point may not be withdrawn and will continue to be used as part of the study.

Research staff may discontinue the subject's participation in this study at any time in the event a protocol deviation or activity is identified by the principal investigator as having the potential to confound the final result.

There are no consequences to discontinuing participation in this study. All discontinuations, and the reason for discontinuation, will be confirmed in writing.

Sources of Materials: Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.

The sources of research materials obtained in this study include the data collected on the Eligibility Checklist, MRI Safety Screening Questionnaire, Data Sheet, as well as the MR imaging.

All data collected during the study is research specific.

DRUG INFORMATION

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [x] **Not applicable**

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source.

N/A

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

N/A

Storage and stability – for both intact and mixed products.

N/A

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

N/A

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also, adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

N/A

Is it FDA approved: (include FDA IND Number)

1. in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.
   N/A
2. for the route of administration specified? If no, provide justification for route and describe the method to accomplish.
   N/A
3. for the intended action?
   N/A

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: Provide rationale for subject selection in terms of the scientific objectives and proposed study design.

Our goal is to clarify whether the brain can be non-invasively cooled by circulating cold water across the surface of the neck. If so, this brain cooling modality could be applied in a variety of clinical settings (*e.g.* stroke, traumatic brain injury, migraine). As a first step, we aim to evaluate this modality of cooling in healthy adults. If effective, we would then plan to study it in other clinical settings.

Vulnerable Populations: Explain the rationale for involvement of subjects (e.g., cognitively impaired, Non-English speaking, prisoners, students). Discuss what procedures or practices will be used in the protocol to minimize their susceptibility to undue influences and unnecessary risk (physical, psychological, etc.).

[x] **Not applicable**

Inclusion/Exclusion Criteria: Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.

Inclusion criteria:

- Healthy adults age 18-65 years

Exclusion criteria:

- Pregnancy
- Contraindications to MRI (e.g. claustrophobia, metallic implants, etc.)
- Signs of ulcerations, burns, hives or rash where the neck wrap is applied
- History of Raynaud's disease, venous or arterial occlusive disease (e.g. carotid stenosis), cryoprecipitation disorders (e.g. cryoglobulinemia) and pernio (also known as chilblains)

Inclusion of Minorities and Women: Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.

Minorities and women will be included without discrimination.

Inclusion of Children: Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study. Provide target accrual for this population. Identify whether children are wards of the state. **If children are excluded** then provide appropriate justification.

Children are excluded because we will be studying an adult-sized neck wrap.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

N/A

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

x **Not applicable**

Will the SONA Psychology Pool be utilized? *Include documentation indicating permission to use this recruiting tool*

Yes [ ] No [x]

FINANCIAL CONSIDERATIONS

Describe all potential research related expenses to subjects:

None.

Compensation for participation: Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.

[ ] **Not applicable**

Subjects will be given $125 after their first intervention and $125 after their second intervention in the form of a check(s). Each visit will take approximately 2.5-3 hours, plus travel time, making this an appropriate amount.

Research Data Management Plan: The Research Data Management and Security Plan form must be completed. The form, along with guidance, can be found in our forms library and must be submitted with your initial application.