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ORIGINAL ARTICLE

Cold Blooded: Evaluating Brain Temperature by MRI During Surface Cooling of Human Subjects

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Abstract
Background Targeted temperature management (TTM) confers neurological and survival benefits for post-cardiac arrest patients with return of spontaneous circulation (ROSC) who remain comatose. Specialized equipment for induction of hypothermia is not available in the prehospital setting, and there are no reliable methods for emergency medical services personnel to initiate TTM. We hypothesized that the application of surface cooling elements to the neck will decrease brain temperature and act as initiators of TTM.
Methods Magnetic resonance (MR) spectroscopy was used to evaluate the effect of a carotid surface cooling element on brain temperature in healthy adults.
Results Six individuals completed this study. We measured a temperature drop of 0.69 ± 0.38 °C (95% CI) in the cortex of the brain following the application of the cooling element. Application of a room temperature element also caused a measurable decrease in brain temperature of 0.66 ± 0.41 °C (95% CI) which may be attributable to baroreceptor activation.
Conclusion The application of surface cooling elements to the neck decreased brain temperature and may serve as a method to initiate TTM in the prehospital setting.

Keywords Targeted temperature management · Therapeutic hypothermia · Cardiac arrest · Magnetic resonance spectroscopy · Cooling collar · Surface cooling

Abbreviations

MRI, MR	Magnetic resonance imaging
TTM	Targeted temperature management
NAA	N-acetylaspartate

Introduction

Despite advances in medical care, survival rates following out-of-hospital cardiac arrests remain devastatingly low, approaching 10 percent [1]. Only a fraction of these patients are ultimately discharged from the hospital with a good neurological outcome [2]. In 2002, two large prospective randomized trials published in the New England Journal of Medicine demonstrated that patients treated with induced mild hypothermia had significantly better neurological outcome and survival rates than patients that did not receive targeted temperature management [3, 4].

Targeted temperature management (TTM) or "therapeutic hypothermia" has become a standard component of care for post-cardiac arrest patients with return of spontaneous circulation (ROSC) who remain comatose [5]. In

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2010, the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care were updated to include a recommendation to cool the body to 33 °C (91.5 °F) or to the range of 32–34 °C (89.6–93.2 °F) for 12–24 h [6]. An additional large clinical trial demonstrated no significant difference in patients who were cooled to 32 versus 36 °C [7]. The most recent guidelines from the American Heart Association recommend cooling the body to 32–36 °C for at least 24 h after cardiac arrest [5].

While different trials have used various cooling methods, target temperatures, and timing of hypothermia, it is generally accepted that cooling should begin as soon as possible [3, 4, 7–11]. However, there are few reliable ways to initiate therapeutic hypothermia in the prehospital setting, which poses a problem in rural locations with long transport times or during interfacility transfers. Infusions of chilled saline by emergency medical services personnel have been attempted in the prehospital setting but were shown to increase re-arrest rate and pulmonary edema, while failing to improve survival or neurological status [9]. More generally, the invasive endovascular procedure tied to infusions of cold saline introduces an additional risk, especially in the prehospital setting [12]. Consequently, the American Heart Association recommends against the routine prehospital cooling of patients after ROSC with rapid infusion of cold intravenous fluids [5].

Prehospital cooling using surface elements applied directly to the neck may be a reasonable option to initiate TTM in these patients during transport to the hospital. Carotid surface cooling has been successful in inducing hypothermia in animal models [13]. In humans, it is not clear if the brain is cooled selectively by carotid cooling or whether the entire body is cooled. Magnetic resonance (MR) spectroscopy provides a noninvasive method to directly measure brain temperature in human subjects [14]. Our aim was to evaluate brain temperature utilizing MR spectroscopy in healthy human subjects during surface cooling of the carotid arteries. We hypothesized that the application of surface cooling elements to the neck would decrease brain temperature and initiate targeted temperature management.

Methods

This investigation was approved by The University of Vermont Institutional Review Board (CHRMS #14-150) and registered with ClinicalTrials.gov (NCT02431026) before commencing subject enrollment. Healthy adults with no contraindications for hypothermia induction or magnetic resonance imaging (MRI) qualified for participation. Informed consent was obtained from all individual participants included in the study. Enrolled subjects completed a physical examination by a licensed physician prior to MRI sessions.

Magnetic Resonance Spectroscopy

Temperature measurements were taken using MR spectroscopy. To extract brain temperature, this technique utilized the difference between the chemical shift of water, which is temperature dependent, and the metabolite N-acetylaspartate (NAA), which is independent of temperature (Fig. 1). Data were acquired using a 3T Philips Achieva dStream MRI scanner. The pulse sequence used was based on single voxel point resolved spectroscopy with TE/TR = 144/2000 ms, 16 averages, 44 s per acquisition. The sequence was modified to provide partial water saturation to enable measurement of both water and NAA reference from the same acquisition. Measurements were derived from the following equation: Temp. °C = 296.1–97.1 (Δwater–N-acetylaspartate).

Method Verification

1. *Controlled temperature verification using a precooled phantom solution*. A precooled water and NAA phantom solution was used to verify system measurements. This solution mimicked water and NAA measured in human brain tissue. The phantom solution was cooled to ~17 °C and then placed in the MRI scanner. As the solution warmed to room temperature, spectroscopy measurements were taken approximately every 1 min.

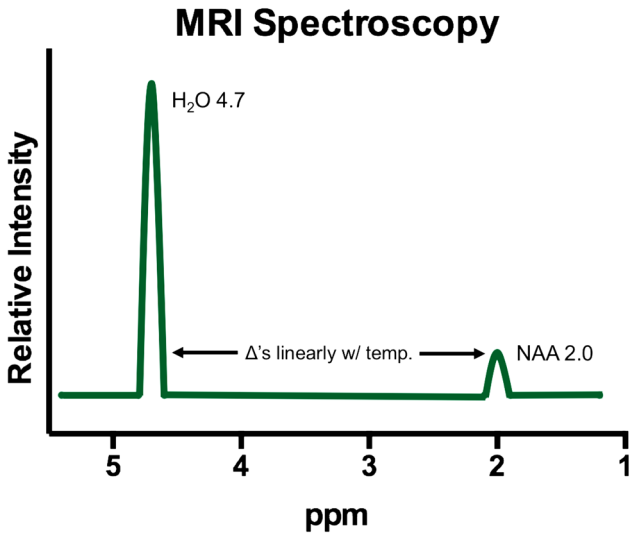

Fig. 1 Representation of magnetic resonance (MR) spectroscopy data. Brain temperature was calculated using: Temp. °C = 296.1–97.1 (Δwater–N-acetylaspartate). The chemical shift of N-acetylaspartate (NAA) is independent of temperature

2. *Evaluation of nonthermal effects of bag placement*. Experimentation was performed to investigate the presence of artifactual temperature changes. Spectroscopy temperature measurements of a water and NAA phantom solution were taken with and without the room temperature element in close proximity. Efforts were made to match the geometry of a human subject; the distance and position of the room temperature element in relation to the measurement voxel were considered. Five spectroscopy measurements were taken without the room temperature element, followed by five acquisitions with the same element in close proximity to the solution. This procedure was repeated four times.
3. *Measurement stability in human subjects*. Preintervention (baseline) temperature measurements were taken approximately every 60 s for the first 10 min of each MRI session.

Evaluating the Effect of a Carotid Surface Cooling Element on Human Brain Temperature

MR spectroscopy was used to evaluate the effect of a carotid surface cooling element (Cryothermic Systems, Inc.) on brain temperature in healthy adults. The cooling element is designed much like a disposable chemical ice pack. It is activated by rupturing an internal chemical pack that is then mixed with the pack contents through physical shaking. The flexible cooling element was activated and then placed on the anterior surface of the neck where it conformed to the individual subject's anatomy. The element's dimensions are $12'' \times 4.75''$. The cooling element is designed to provide 20 min of continuous cooling. Consecutive application of two elements was measured to maximize the potential to detect a drop in temperature.

Randomization with a random number generator (Excel, Microsoft Corp.) dictated the order in which each subject received 40 min of the cold (−4 °C) or room temperature (21 °C) elements. Before and after each subject underwent 40 min of element application, ten additional measurements were taken with no element in place. All MR spectroscopy measurements were taken approximately every 60 s to determine the brain temperature in the fronto-parietal white (Fig. 2). It should be noted that a 1-min approximation exists because the measurement frequency was dependent on the amount of time required to complete each MRI sequence (approximately 60 s). MRI sessions with either the cold or room temperature element were scheduled at least 10 days apart.

Statistical Approach

Each individual subject served as their own control, with baseline data collected over a 10-min period, for comparison to temperatures measured during the intervention period. Group results were compared using a Wilcoxon ranked sum test.

Results

Results of Method Verification Techniques

1. When the temperature of a precooled phantom solution was assessed with MR thermometry, precise and expected data confirmed verification (Fig. 3).
2. Evaluation of nonthermal effects of bag placement yielded an artifactual temperature change that was less than 0.2 °C with a general upward trend.

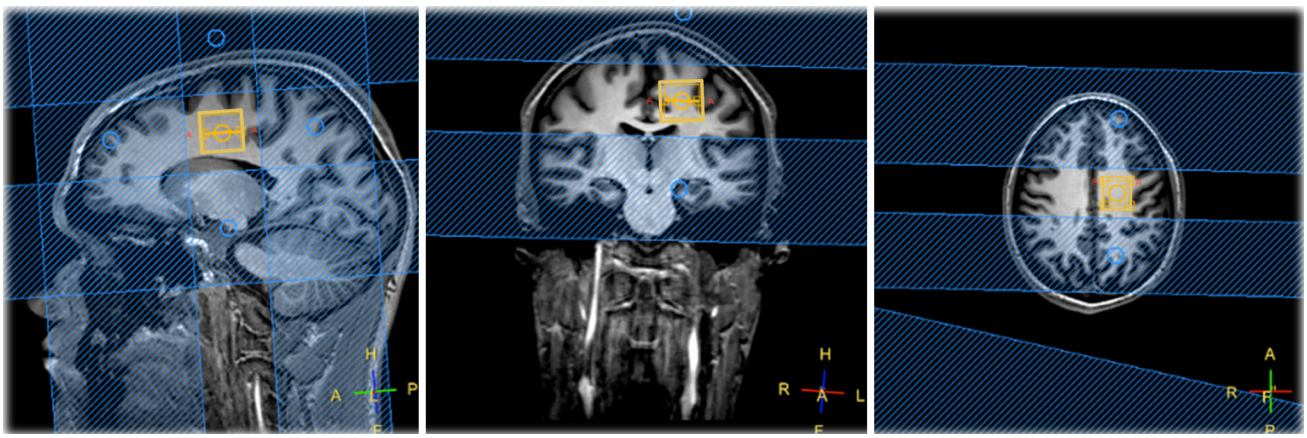

Fig. 2 MR spectroscopy voxel placement in the fronto-parietal white matter of the human brain

3. Measurements of stability in human subjects during baseline measurements were consistently stable (see appendix data).

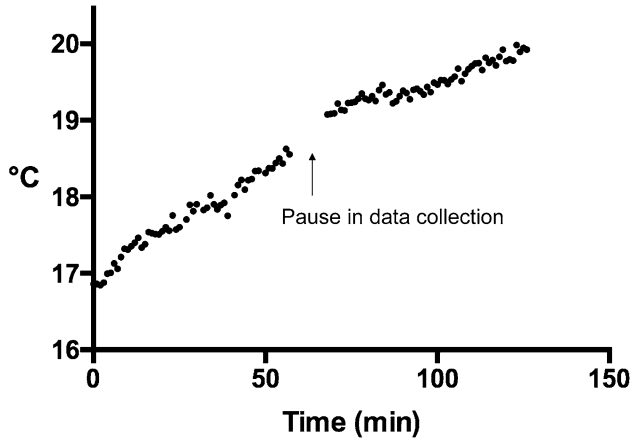

Fig. 3 Verification of magnetic resonance imaging (MRI) measurements using phantom solution. MRI temperature recordings of a precooled water and N-acetylaspartate (NAA) phantom solution as it reached room temperature

Ten healthy adult subjects were consented for this study. The first four subjects were utilized to pilot the protocol and establish optimal conditions for MR spectroscopy. A total of six subjects were then studied under standardized conditions as described in our methods, with appropriate controls; these six subjects were used for analysis. The respective mean age and body mass index were 33 years (SD = 15) and 24 kg/m^3 (SD = 3). A Wilcoxon signed-rank test yielded a significant ($p < 0.05$) cooling effect with both the cold and room temperature elements (0.69 ± 0.38 and 0.66 ± 0.41 °C [95% CI] average decrease from baseline, respectively) (Figs. 4 and 5). There was no significant difference in temperature drop magnitude between the two elements. Cooling occurred approximately one minute from time of element application. Throughout the length of the scan, average axillary temperature across the six subjects was 36.14 ± 0.58 °C; heart rate was 59.68 ± 6.09 beats per minute; systolic blood pressure and diastolic blood pressure were 121.01 ± 8.20 and 69.92 ± 4.95 mmHg, respectively (95% CI).

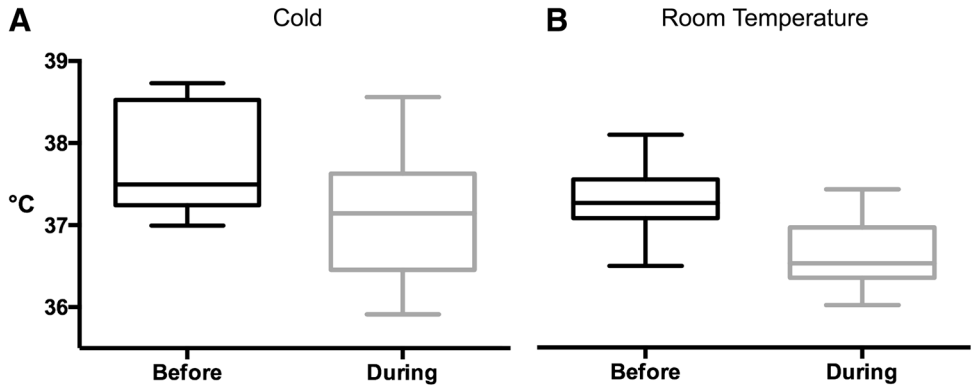

Fig. 4 Comparing cold and room temperature elements in human subjects before and during application of elements. Comparison of magnetic resonance (MR) brain temperature measurements before and during the application of **a** cold elements and **b** room temperature elements. Multiple measurements for individual subjects were compiled; figure shows the combined results for all subjects ($n = 6$)

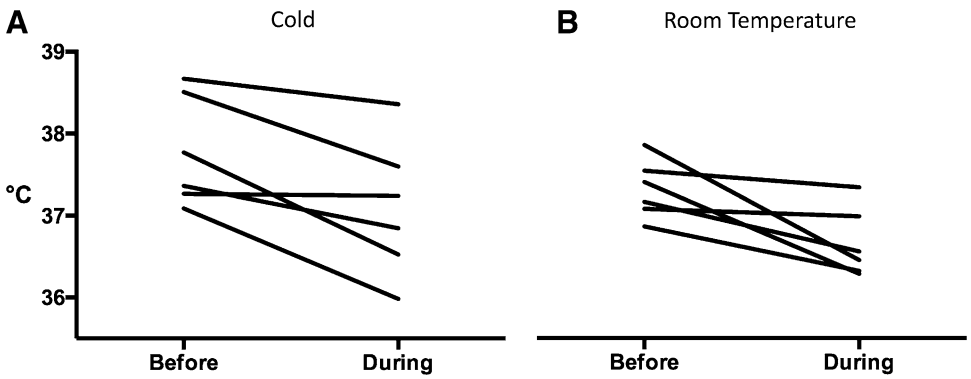

Fig. 5 Comparing cold and room temperature elements in individual human subjects before and during application of elements. Comparison of average magnetic resonance (MR) brain temperature measurements before and during the application of **a** cold elements and **b** room temperature elements. *Each line* represents a single subject ($n = 6$)

Conclusion

Hypothermia is thought to play a neuroprotective role by reducing the inflammatory response following injury, lowering metabolic demand, and decreasing the release of excitatory neurotransmitters, among other mechanisms [15–17]. Clinical investigations support the use of TTM to improve survival and neurological outcomes after cardiac arrest [3, 4, 7, 10]. However, the initiation and maintenance of cooling pose problems for emergency medical service providers, especially in rural areas with long transport times, or during interfacility transfers.

We hypothesized that the application of surface cooling elements to the neck would decrease brain temperature and therefore may serve to initiate targeted temperature management. The present work demonstrated an effect on brain temperature. This is an important contribution to the literature. While some hypothermia experiments have directly measured brain temperature in animal [13] or human subjects [18–21], most clinical trials have used core temperature measurements alone [3, 4, 7–11], and none have utilized MR spectroscopy as a method to measure brain temperature.

However, we had an unexpected observation: the application of room temperature elements to the neck, intended as a control for the cold elements, also dropped brain temperature. This observation calls into question the mechanism of action of carotid surface cooling devices. Even a room temperature (21 °C) element could provide a heat transfer effect from the body to the comparably cooler element. Another possible mechanism to explain the decrease in brain temperature with both room temperature and cold elements applied to the neck includes the activation of baroreceptors. Previous studies have shown that direct stimulation of the carotid baroreceptors in rats decreased core temperature [22]. Finally, positioning in a supine posture in humans alone can cause a slight decrease in core temperature [23]. These combined mechanisms may have contributed to this experiment's observed effects on brain temperature in human subjects. Future investigation should be directed toward further elucidation of these effects. Specifically, the relationship between carotid baroreceptor stimulation and temperature regulation in humans warrants additional study.

Interestingly, the present work coincides with the results of a recent animal model feasibility study that utilized a carotid cooling device. Here, a 0.6 °C/h decrease in sheep brain temperature was observed upon application of the cooling device. Moreover, the investigators fitted their experimental data to a thermodynamic model and predicted a 0.64 °C/h cooling rate for the brain of a 70-kg adult human subject [13]. This prediction closely aligns with the results of the present experiment.

Furthermore, the device in this study did not result in any noticeable effect on axillary skin temperature, blood pressure, or heart rate, unlike comparable surface cooling devices [24]. This may suggest a lower risk of negative side effects compared to other present methods of hypothermia induction [9, 12, 19].

This study included a number of limitations. It is important to consider the substantial differences in post-cardiac arrest physiology compared to that of a healthy subject. Individuals who have recently suffered cardiac arrest may experience diminished thermoregulation activities and as a result, be more susceptible to the cooling interventions examined in the present work. It should be noted that the results of this study indicate that surface cooling alone is insufficient to reach clinical targets of 36 °C or lower and instead may be designated specifically for the initiation of targeted temperature management.

Furthermore, the possible introduction of artifactual temperature changes exists as a potential limitation. Phantom experimentation yielded a less than 0.2 °C artifactual fluctuation with a general upward trend. This observation may have resulted from temperature differences in the scan room or from radiofrequency absorption (unlike a human head, the phantom solution is thermally isolated and contains no thermoregulation). As such, the degree of artifactual influence should be further explored in subsequent studies. Finally, an observed increase in heterogeneity of baseline temperatures in the cold element sessions should be noted as a potential limitation.

While early initiation of targeted temperature management presents a method to improve survival and neurological outcomes after cardiac arrest, clinical investigations studying out-of-hospital hypothermia induction produced conflicting results [4, 9]. It is possible that the specific technique used to induce hypothermia accounted for their diverging findings. As such, the utilization of a simple and convenient carotid surface cooling device may provide a standardized mechanism to initiate targeted temperature management in the prehospital setting.

In conclusion, this novel investigation successfully evaluated core brain temperature during carotid surface cooling of human subjects. Future studies should consider the use of noninvasive MRI thermometry to evaluate the effectiveness of surface cooling and other methods of targeted temperature management.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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