

## ORIGINAL RESEARCH

# Novel intracranial brain cooling catheter to mitigate brain injuries

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Received 28 November 2010

Revised 24 February 2011

Accepted 4 April 2011

Published Online First

14 June 2011

## ABSTRACT

**Background** The neuroprotective effects of cooling the spinal cord in a sheep model by a self-contained intrathecal catheter was reported recently by the authors. The present study was designed to determine if cooling catheters in the lateral ventricles of the brain can effectively cool the CSF and thereby reduce brain temperature while maintaining systemic normothermia.

**Methods** The cooling catheter is a self-contained system that circulates a cold fluid and cools the CSF that circulates in the brain. The CSF in turn cools the surrounding brain by conduction. Burr holes were made in the skull and the catheter was placed into the lateral ventricles using the standard method for placement of ventriculostomy catheters. To monitor the cooling effect, four temperature probes were placed in the brain (left and right hemispheres of the brain in anterior and posterior locations to the ventricles).

**Results** Five experiments were successfully completed. The mean brain temperature for all sheep decreased to 34.5°C (mean) during the 3 h cooling period (9.7% reduction from baseline brain temperature of 38.2°C). Cooling fluid was circulated through the catheter at a rate of 50 ml/min. The lowest achieved brain temperature during cooling was 26.7°C. When cooling was stopped, the brain temperature readings equilibrated with the core temperature promptly. Post mortem examination of the brains showed no morphologic changes under gross or histologic examinations.

**Conclusion** Localized cooling of the brain to moderate hypothermic levels while maintaining relative systemic normothermia was demonstrated in an animal model with intraventricular cooling catheters.

## INTRODUCTION

Stroke, traumatic brain injury (TBI) and cardiac arrest are three major sources of significant neurological morbidity. Each year there are 4.5 million people who survive a stroke, of whom more than a million have significant neurological dysfunction.<sup>1</sup> TBI occurs in more than 1.4 million Americans every year, and has left an estimated 5.3 million Americans with permanent disability.<sup>2</sup> Approximately 70 000 patients per year in the USA are resuscitated from cardiac arrest but less than 10% fully recover to their baseline level of function.<sup>3</sup>

Many studies have shown that hypothermia can protect against ischemic neuronal injury.<sup>4</sup> Indeed, induction of systemic hypothermia is an accepted initial step in the management of patients who

survive cardiac arrest.<sup>4 5</sup> Also, hypothermic neuronal protection underlies the fascinating and widely applied technique of deep hypothermic circulatory arrest used for decades in surgical procedures on the aortic arch.<sup>6 7</sup>

Despite its clear therapeutic benefit, *systemic* hypothermia is associated with side effects that have limited its use in modern medical practice. Notable side effects of systemic hypothermia include bleeding diathesis, shivering, arrhythmias, suppression of the immune system with increased susceptibility to infection and electrolyte imbalance.<sup>8</sup> As current cooling methods are not ideal, there is much interest in developing a technique that would provide the neuroprotective benefit without the significant side effects of global, systemic hypothermia.<sup>9</sup>

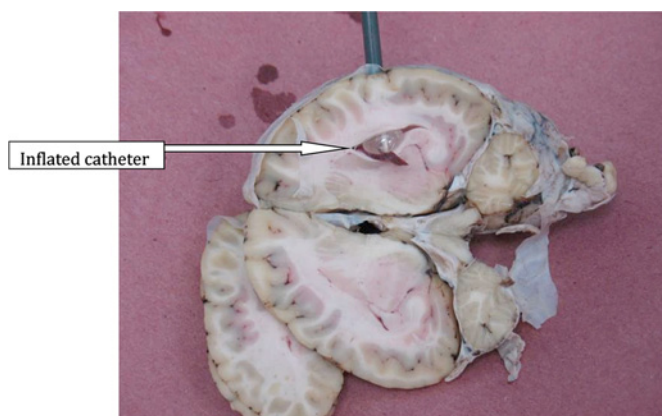
We set out to investigate the efficacy of cooling the brain *topically*, using a self-contained cooling catheter that is inserted into a lateral ventricle of the brain. In a previous study, our group demonstrated effective localized cooling of the spinal cord by inserting a similar catheter into the intrathecal space and cooling the CSF surrounding the spinal cord.<sup>10</sup> Building on the successes of the spinal cord experiments—in which average spinal cord temperatures were reduced by 6.3°C (−17.1% from baseline)—the current investigation aims to apply topical intracranial cooling to the brain (via cooling the intracranial CSF). We believe this technique would offer an alternative method of providing hypothermic protection from ischemic neuronal injury without the deleterious effects of inducing systemic hypothermia.

## MATERIALS AND METHODS

### Catheter

A catheter was designed for our experiment in conjunction with Synectic Inc (Milford, Connecticut, USA). This brain cooling catheter evolved from the device we had used for spinal cooling. We developed the catheter based on brain models and subsequently autopsy specimens.

As shown in figure 1 and figure 2, the catheter is placed in the lateral ventricle using a ventriculostomy/burr hole approach. This technique of accessing the lateral ventricles is consistent with standard clinical care in neurological intensive care units and emergency rooms throughout the world for drainage purposes. The catheter is an 8 F polyurethane device with two lumens that communicate at the distal end in a distensible wrap-around sac. Supersaturated saline solution from a cold



**Figure 1** Ex vivo demonstration of novel topical cooling catheter in place in a sheep brain. Note how self-expanding chamber expands to the limits of the lateral ventricle, maximizing the potential for heat transfer.

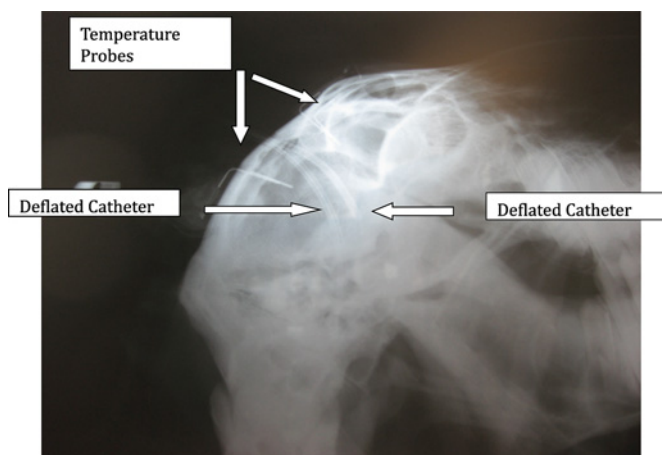
reservoir is pumped through the inlet lumen of the catheter, circulates through the distensible sac and returns via the outlet lumen to a run-off container. Because it is a closed circuit, the saline never communicates with the CSF and has no direct contact with the subject. The cold saline is kept at a temperature of  $-7^{\circ}\text{C}$  to  $-10^{\circ}\text{C}$  and is circulated at a flow rate of 36–50 ml/min.

#### Experimental model

We conducted the experiments in adolescent sheep. We chose this model because the sheep brain is a reasonable structural proxy for humans with respect to size and location of the ventricular system, and because we have significant experience relating to therapeutic cooling with this species from our previous spinal cooling study.

#### Experimental procedure

All experiments were approved and monitored by the Institutional Animal Care and Use Committee. The animals were sedated with acepromazine 0.5 mg/kg intramuscularly and valium 0.5 mg/kg intravenously, followed by ketamine 2.2–2.75 mg/kg intravenously and then intubated. Anesthesia was maintained at an adequate level with isoflurane throughout the procedure. A sagittal scalp incision was made, revealing the posterior fontanelle and coronal suture. Burr holes were made



**Figure 2** Post mortem x-ray of sheep skull with placement of cooling catheters and temperature probes.

bilaterally, 1.5 cm anterior and 1.5 cm lateral to the posterior fontanelle at an angle of  $10^{\circ}$  from the sagittal plane on each side. A pediatric slotted stylet was inserted into each hole, and location in the lateral ventricle was confirmed by flow of CSF and pressure differences measured by manometry. The cooling catheters were placed via the burr holes in both the right and left ventricles. Temperature probes (Smiths Medical Level 1 Myocardial Temperature Sensor, Ref# MTS-TC15) were placed in four locations within the brain parenchyma: anterior and posterior to the ventricles on both sides of the brain. Systemic temperature was measured using both a rectal probe and a nasopharyngeal probe (figure 3).

The cooling catheter was then activated for 3 h, followed by a 2 h period during which no fluid was circulated in the ventricles. During this 5 h block, temperature readings were recorded every 5 min for the first 15 min and every 15 min thereafter from each probe. Vital signs were monitored throughout.

At the end of the 5 h period, the animals were euthanized using Euthasol 1 ml/5 kg intravenously. X-rays were then taken of the animals' brains. Gross and microscopic post mortem examinations of the animals' brains were also performed. A total of five experiments were conducted.

## RESULTS

### Technical performance

All five experiments were successfully executed. In each sheep, cooling catheters were accurately inserted into the right and left ventricles and functioned as designed. Temperature data of the brain cooling were collected from the cerebral temperature probes as well as systemic temperature from the rectal and nasopharyngeal monitors. The animals were continuously monitored by licensed veterinarians and medical technicians and tolerated the experiments with no signs of distress. The experiments proceeded well for the 5 h duration of each study, without technical problems or incidents.

### Effectiveness of cooling

All five experiments demonstrated effective brain cooling while maintaining systemic normothermia. Figure 3 shows the averaged core body and brain temperature results from all five experimental trials.

Within 5 min of the commencement of the experiment, cooling of the brain was effected in all five sheep. Furthermore, core body temperature remained relatively normothermic, with only a 1.4% drop from baseline ( $38.3^{\circ}\text{C}$  to  $37.5^{\circ}\text{C}$ ) for the five trials.

Cooling effects from each trial are summarized in table 1. The mean baseline brain temperature for all sheep was  $38.2^{\circ}\text{C}$ . The mean brain temperature during cooling was  $34.5^{\circ}\text{C}$ , a cumulative change of 9.7%. The greatest cooling effect was demonstrated in trial 4 where the mean brain temperature fell to  $31.4^{\circ}\text{C}$ , a change from baseline of 15.1%. The smallest cooling effect was a 3.6% change from baseline in trial 2. The lowest temperature recorded in a single reading was  $24.9^{\circ}\text{C}$ .

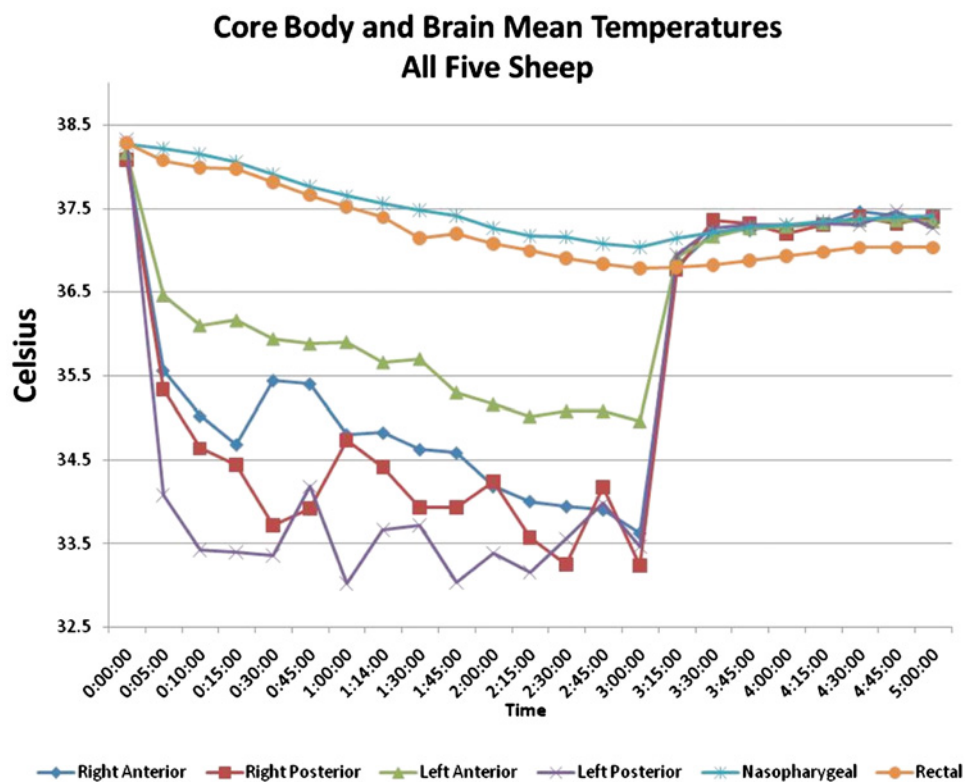
All brain temperatures showed recovery to baseline temperature within 15 min of discontinuation of the cooling process.

### Post mortem examination

During post mortem examination, all brains were examined for identifiable tracts to the ventricles from insertion of the cooling catheter. These were confirmed. There was no evidence of gross damage to the ventricles in any of the sheep experiments. Histologic analysis using haematoxylin–eosin preparations was

## New devices

**Figure 3** Mean cooling catheter readings compared with core body temperatures.



done on all post mortem harvests of the sheep brains at multiple sections corresponding to the placement of the temperature probes as well as the cooling catheters. No morphologic changes were observed due to thermal effects of the cooling catheter. Figure 4 is a representative histologic image, demonstrating no evidence of cellular damage.

## DISCUSSION

Although the exact mechanism is still a topic of debate, it is well understood that ischemia causes neuronal damage through several pathophysiologic pathways, including energy depletion, calcium influx, membrane damage, formation of free radicals and activation of protein kinases.<sup>2</sup> Hypothermia protects the brain from ischemic changes by decreasing metabolic demands and thus the need for oxygen.<sup>5</sup> Further, hypothermia decreases production of oxygen free radicals, minimizing damage to the cell membrane.<sup>11</sup>

Direct brain cooling, the concept of cooling brain matter selectively, is an active area of research.<sup>12</sup> There have been several recent attempts at cooling the brain directly through topical garments worn on the head, as well as nasopharyngeal cooling through direct air flow.<sup>13</sup> Both techniques yielded

modest results, highlighting the need for a novel, more effective technique.

While the optimal degree of cooling is still actively debated, it has been shown that the metabolic demand of the brain tissue is decreased substantially by cooling brain tissue, even by  $<1^{\circ}\text{C}$ .<sup>14</sup> Thus our initial results are promising as we demonstrated a substantial decrease in brain temperature while maintaining systemic normothermia.

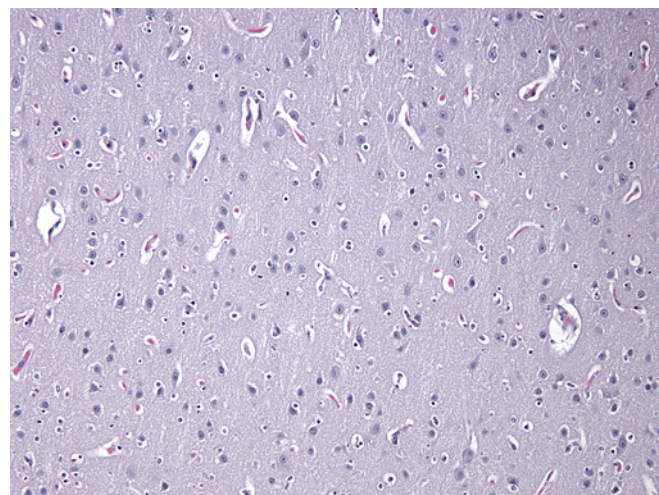
Potential applications of this technique may encompass any insult that results in brain ischemia or injury, including but not limited to ischemic stroke, TBI and cardiac arrest.

## Limitations

There is room for improvement and adaptation of our technique. One limitation of our study is that the degree of cooling from

**Table 1** Summary of Temperature changes in all experiments

	Mean brain temperatures ( $^{\circ}\text{C}$ )					
	Sheep 1	Sheep 2	Sheep 3	Sheep 4	Sheep 5	All sheep
Baseline brain temperature	38.7	38.8	38.2	37.5	37.8	38.2
All cooling values (mean)	33.4	37.3	33.8	31.8	36.0	34.5
Temperature decrease from baseline ( $^{\circ}\text{C}$ )	5.4	1.4	4.4	5.7	1.8	3.7
% Temperature decrease	-13.9	-3.6	-11.4	-15.1	-4.7	-9.7



**Figure 4** Cerebral tissue, showing no evidence of hypothermic tissue damage.



## Key messages

- ▶ It is well known that hypothermia is protective for the brain but systemic cooling has major drawbacks.
- ▶ Novel and effective methods for topical cooling of the brain are needed.
- ▶ We report animal application of a new method for topical cooling of the brain using catheters placed into the lateral ventricles of the brain; coolant recirculates within the catheters themselves, without mingling with the CSF.
- ▶ This study demonstrates that substantial cooling of the brain is indeed achieved by this novel system.
- ▶ This experimental system holds promise for mitigation of traumatic and ischemic injuries of the brain, including post-resuscitation anoxic injury.

experiment to experiment was not uniform. Over the five experiments, the average cooling ranged from  $-3.6\%$  to  $-15.1\%$  from baseline. We speculate that improvements in placing the catheter in the ventricle as well as more consistent flow rates could reduce the variability. We have already refined our catheter delivery apparatus in response to the potential difficulties in achieving and confirming proper placement in the lateral ventricles of the brain. That being said, this pilot trial successfully demonstrated the ability to cool the brain using this novel technique, and future trials will aim to improve the technical consistency and accuracy of this cooling technique.

Another aspect which we plan to investigate relates to the system's cooling efficiency in specific areas of the brain. We wish to study the 'cooling wave' emanating from the cold intraventricular catheter by more sophisticated means, with modern MRI, positron emission tomography scan or other thermal imaging techniques. Understanding this cooling dynamic as it relates to neuroprotection could prove valuable in addressing specific types of brain injury.

Furthermore, this study did not include any opportunity to demonstrate a salutary effect of our cooling. We wished in this pilot study to demonstrate the technical feasibility of cerebral cooling by this novel intraventricular catheter, reserving demonstration of efficacy for future animal studies involving a brain insult.

## CONCLUSIONS

This experiment documents the technical feasibility of direct, topical intracranial brain cooling by a specially designed intraventricular cooling catheter; the direct brain cooling is achieved

while maintaining systemic normothermia. This device and technique hold promise for decreasing neuronal injury in a variety of ischemic insults.

**Funding** This research has been supported by Phase I and Phase II STTR grants from the National Science Foundation.

**Competing interests** JS and JAE are principals of Coolspine Inc, a very small Yale University start-up company developed to advance these topical cooling technologies. There are no commercial products and no near-term plans for such.

**Ethics approval** All experiments were approved and monitored by the Institutional Animal Care and Use Committee.

**Contributors** All authors contributed substantially. RMM conducted the experiments and wrote the first draft of the paper. GG conducted the experiments and brought neurosurgical expertise. Dr Solomon assisted in the experiments. JS assisted in the experiments and in the development and implementation of the device. DB participated in the experiments. JAE developed the device, conceived the experiment, participated in portions of the experiments and participated significantly in the writing of the manuscript.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*J NeuroIntervent Surg* 2012 4: 130-133 originally published online June 14, 2011

doi: 10.1136/jnis.2010.004432

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