

AD _____

Award Number: W81XWH-11-2-0134

TITLE: A novel method for inducing therapeutic hypothermia in a swine model of blast-induced traumatic brain injury with associated hemorrhagic shock

PRINCIPAL INVESTIGATOR: Matthew M. Kumar, MD

CONTRACTING ORGANIZATION: Mayo Clinic, Rochester, MN 55905

REPORT DATE: May 2012

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE 01-05-2012		2. REPORT TYPE Final		3. DATES COVERED 18 April 2011 - 17 April 2012	
4. TITLE AND SUBTITLE A novel method for inducing therapeutic hypothermia in a swine model of blast-induced traumatic brain injury with associated hemorrhagic shock				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-11-2-0134	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Matthew M. Kumar, MD. E-Mail: mkumar@mayo.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Mayo Clinic Rochester, MN 55905				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The purpose of this study was to determine the effect of rapidly induced hypothermia on neurological outcomes following fluid percussion injury in swine. A second objective was to test the safety and efficacy of inducing hypothermia through augmented heat extraction from the lungs using heliox and perfluorocarbon mist ventilation. The hypothermia device was built and bench tested. Brain temperatures in all hypothermic animals reached target (32-33°C) within 60 minutes. We standardized the anatomical location and fluid force necessary to create consistent severe brain injury in pigs. Seven of the eight hypothermic and four of the eight normothermic animals survived to the end of the five-day study. Hypothermia effectively prevented the gradual rise in intracranial pressure. Neurological and behavioral scores were better in the surviving normothermic animals on day #3; however these differences disappeared by day #5. The results of serum biomarkers for brain injury and histopathological scores are being processed. The study was extended by six months due to the additional safety and feasibility requirements placed by Mayo IACUC and the inclusion of serum biomarkers into the protocol. If additional funding becomes available, the investigators will add a third arm to the study consisting of blast injury plus hemorrhagic shock.					
15. SUBJECT TERMS therapeutic hypothermia, traumatic brain injury (TBI)					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	15	USAMRMC
19b. TELEPHONE NUMBER (include area code)					

Table of Contents

INTRODUCTION:	4
BODY:	4
KEY RESEARCH ACCOMPLISHMENTS:	10
REPORTABLE OUTCOMES:	11
CONCLUSIONS:	11
FUTURE DIRECTIONS:	11
REFERENCES:	12
APPENDIX:	14

INTRODUCTION:

Traumatic brain injury (TBI) remains a significant cause of mortality and morbidity in military and civilian life. The use of therapeutic hypothermia in the treatment of TBI remains controversial and clinical trials report conflicting outcomes [1, 2]. The negative human studies often contradict animal studies which show salutary effects of hypothermia [3, 4]. In order to overcome the poor outcomes of delayed induction of hypothermia (>4.3 hours for enrollment), the National Acute Brain Injury Study: Hypothermia II (NABISH-II) trial excluded patients who could not be enrolled within 2.5 hours of injury [5]. While the trial did not show improved outcomes with hypothermia, the problem may not be the time to induction but the time to reach target temperature following injury. In NABISH-I [1], the time to target temperature was greater than 12 hours and in NABISH-II it was 6 hours. Time is of the essence in reaching the target temperature following brain injury—six hours is a significant delay given the exquisite sensitivity of neurons to hypoxemia. Such an assertion is bolstered by the finding that mortality following cardiac arrest increases by an estimated 20% for every one-hour delay in reaching the target temperature [6]. Despite the need for a rapid induction technology, the current methods are slow, cumbersome, unreliable or highly invasive. To meet this need for an effective, non-invasive hypothermia technology, the investigators propose a novel method for rapid induction of hypothermia using the lungs as a heat exchanger. Using an inhalant of perfluorocarbon (PFC) mist and heliox, evaporative cooling is achieved through the lungs. We report on the preliminary findings of the use of this technology in resuscitation following severe lateral fluid percussion injury in swine. Brain histopathology and serum biomarker measurements are currently underway.

BODY:

SOW: Task 1 (3 months): Building hypothermia device

The investigators have successfully accomplished this task. A prototype of the ventilator device capable of inducing hypothermia in large animals has been built and bench tested. The device consists of a ventilator capable of delivering cooled respiratory gases and aerosol PFC into the respiratory tract. A gas blender regulates the heliox concentration. The refrigeration chamber is in-line with the inspiratory limb of the breathing circuit. A pneumatic pressure-driven atomizer generates PFC aerosol within the breathing tube. The PFC vapors are captured by a condenser located in the proximal expiratory limb. A computerized electronic motherboard (master controller) synchronizes the aerosol delivery with the inspiratory phase of the ventilator. Temperature probes embedded inside the breathing circuit provide feedback on the temperature of the inspiratory gases. All of the components are assembled from off-the-shelf products marketed to food or medical industries in the US. The computer is programmed using LabVIEW® (National Instruments, Austin, TX). A detailed description of the device was disclosed to Mayo Medical Ventures (Mayo Tech ID# 2011-134) (Figure 1).

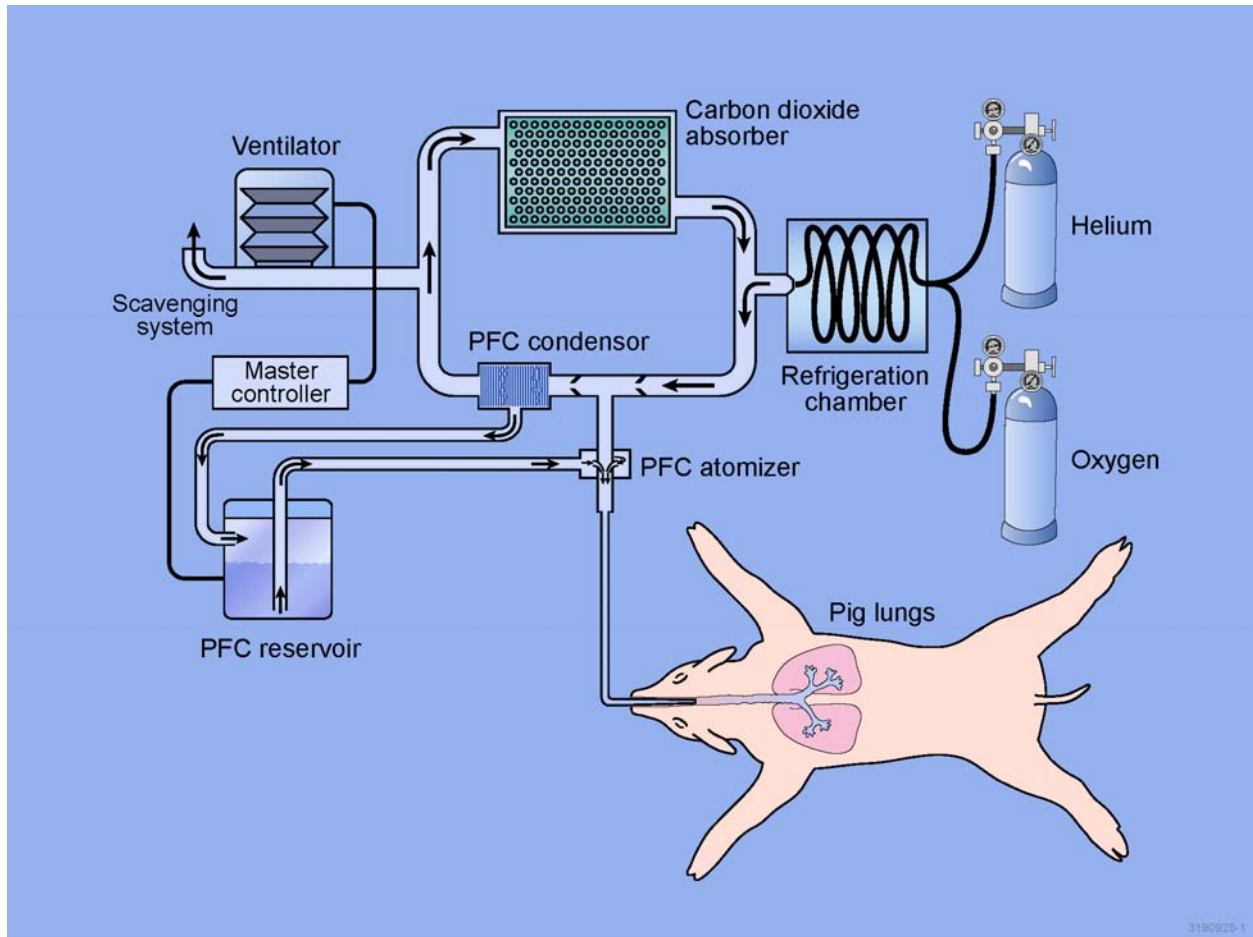


Figure 1

The safety and efficacy of the device was first tested in four animals. The rates of cooling at various core temperature measuring sites are shown in the graph (Figure 2). In these animals, heliox-PFC aerosol ventilation did not produce discernible changes in pulmonary mechanics, arterial blood gases or cardiac function. At necropsy, all vital organs, particularly the tracheobronchial tree and the lung parenchyma, were normal. Histopathology of the lungs was read as normal by a qualified veterinary pathologist.

Factors impacting the rate of cooling in various organs are complex and beyond the scope of the present study. In addition to the augmented heat loss from the lungs, the body continues to lose heat through surface radiation, conduction, convection and evaporation. However, the brain temperature is primarily determined by intra-brain heat production and dissipation by cerebral blood flow [7]. Direct heat loss from the brain to the environment is minimal under normal indoor conditions. Since brain cooling is primarily through perfusion, we see a temperature lag between the pulmonary artery and the brain. Due to the thermal mass of the blood, the brain continues to cool for several minutes after the discontinuation of the pulmonary cooling. Depending on the blood flow, insulation and exposure to external environment, the core temperatures cooled at the following rates (Figure 2).

Tympanum > Esophageal > Pulmonary Artery > Nasopharyngeal > Brain > Bladder > Rectum

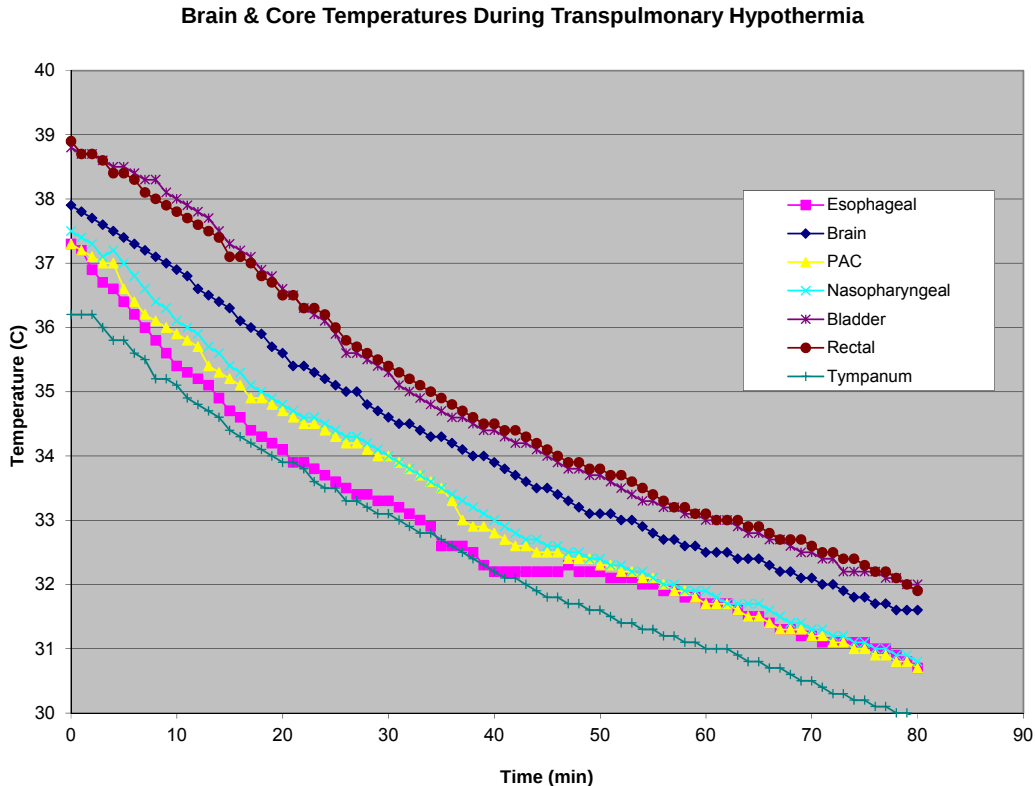


Figure 2

SOW: Task 2 (1.5 months): Creation of swine model of TBI

The investigators have successfully accomplished this task. A fluid percussion injury (FPI) device was procured from a commercial vendor (Dragonfly Research and Development, Inc., Ridgeley, WV), fitted with appropriate non-compliant tubing, and bench tested to deliver pulse pressures ranging from 0.1-15 ATM, lasting 10-500ms in duration. The crucial questions were: (1) what is the ideal location for the surgical placement of the burr hole and the epidural bolt? and (2) how much force is necessary to induce severe brain injury without causing significant hemorrhage, laceration of the brain, or death?

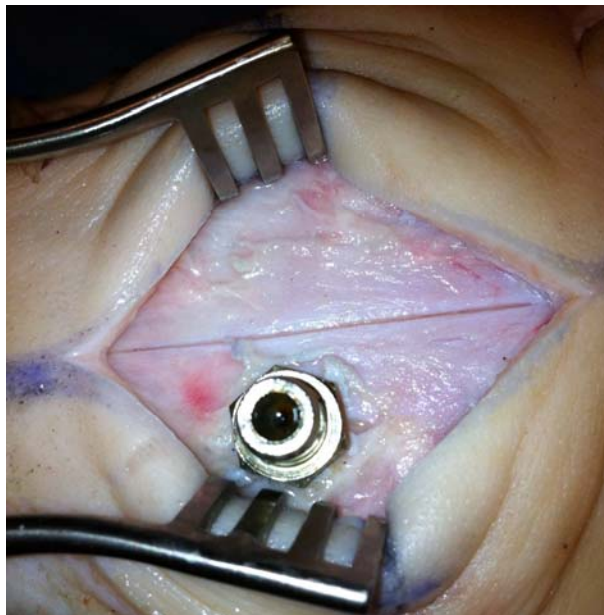


Figure 3

(i). Surgical location of the burr hole and the epidural bolt. There is scant information in the literature regarding the proper location of the burr hole for safe placement and effective administration of a fluid percussion pulse, particularly in pigs. We dissected 16 pig carcasses, made anatomical measurements, and performed X-rays and CT scans on the skulls to determine the appropriate location for the burr hole. We used a probe placed in the opposite lateral ventricle to measure the force

transmitted into the brain. We found the superior sagittal sinus to range in width from 1.8 -6.4 mm in the parietal region. In order to avoid pulsing the sinus and causing inadvertent hemorrhage, the medial margin of the burr hole should be at least 3.2 mm away from the midline. Laterally, the calvarium quickly increases in thickness and curvature, progressing from 10 mm at 1 cm lateral to 14 mm at 3 cm lateral. Hence, bolts placed more laterally tend to impact the dura tangentially rather than perpendicularly. We also found frontal location of the burr hole to cause limited injury, with significant dampening of the pulse (87% less force at the opposite ventricle) as it travels through the brain parenchyma. In contrast, parietal location of the burr hole caused significant injury to the side of the brain where the pulse is applied, with less dampening of the pulse (63% less force at the opposite ventricle) to the opposite side and the infratentorial regions. In addition, we could identify the coronal suture following limited dissection of the scalp in only 3 of the 16 carcasses. In this regard, we found a slightly caudally curved line drawn to connect the posterior orbital margins to lie within a few millimeters of the coronal suture. In summary, we found the ideal location for the insertion of a 6-mm diameter screw type epidural bolt to be 0.7 cm caudal to a posterior inter-orbital line and 1cm lateral to the midline. Such a burr hole avoids causing hemorrhage from the superior sagittal sinus and places the long axis of the bolt more perpendicular to the surface of the parietal dura (Figure 3).

(ii) Force necessary to induce severe, non-lethal brain injury: The goal of this task was to determine the amount of pulse force needed to cause clinically discernible brain injury yet not result in death. Domestic cross-bred pigs, 4 months of age and weighing 38-42 kg, were used in the study. Based on prior literature [8, 9] and the size of the animals, the investigators chose three pressure levels (3, 5, and 7 ATMs) applied for 100 ms each. Histologically, all animals showed the occurrence of diffuse axonal injury. Clinical findings and serum enolase levels were more discriminatory and are shown in Table 1 below.

FORCE	BURR HOLE LOCATTION	NEUROLOGIC DEFICIT	MACROSCOPIC BRAIN INJURY	SERUM ENOLASE (NSE) LEVEL ng/ml			
				0hr	3hr	6hr	24hr
3 ATM	Left Parietal	Right hind leg transient paresis	Contusion left parietal lobe	0.34	1.12	0.92	2.89
5 ATM	Left Parietal	Both hind legs longer paresis	SAH and contusion both parietal lobes	0.48	2.23	2.66	5.60
7 ATM	Left Parietal	Coma All four legs paresis	SAH and contusion both parietal, both temporal lobes and brain stem	0.15	0.18	2.41	11.25

Table 1

At 3 ATM injury level, the animal awoke from anesthesia uneventfully, showing mild weakness in the right hind leg which returned to normal strength by the following morning. At 5 ATM injury level, the animal's conscious level was impaired for several hours following recovery from anesthesia. Both hind legs were significantly weak, with persistent weakness in the right hind leg 24 hours after the injury. At 7 ATM injury level, the animal remained comatose for several hours, unable to assume sternal recumbency and unable to move its legs. The animal did not survive to 24 hours. In all three animals, serum enolase was elevated, showing a significant rise at 24 hours in the 5 ATM animal and in the terminal draw from the 7 ATM animal.

Based on the findings in this phase of the study, the investigators chose to use a left parietal burr hole and 5 ATM pulse pressure for creating TBI in the main study.

SOW: Task 3 (6 months): Hypothermia animal study

The investigators have successfully completed this task. Eight animals in the study group (hypothermia) and eight animals in the control group (normothermia) were subjected to an FPI of 5 (4.7 – 5.3) ATM pulse pressure for 100 ms. In the study group, transpulmonary hypothermia was initiated within 30 minutes following the injury and maintained between 32-33°C for 36 hours. After the period of hypothermia, the animals were allowed to gradually rewarm at no more than 0.8°C per hour over the next 6-12 hours. All animals reached target temperature within 90 minutes of the injury. The rate of brain cooling is shown in Figure 4.

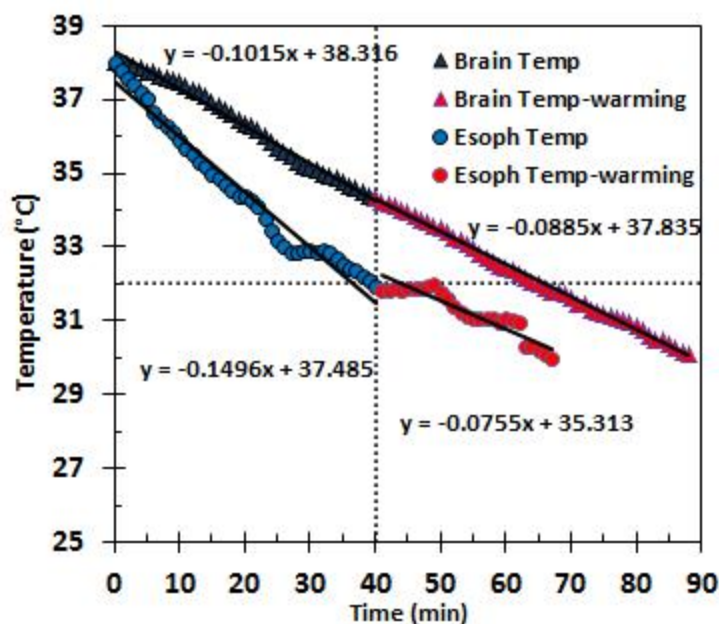


Figure 4

Following induction of hypothermia, the hypothermic temperature was maintained using a combination of a water circulating blanket (Cincinnati Sub-Zero Products, Inc., Cincinnati, OH) and a warm air blanket (Arizant Healthcare Inc., Eden Prairie, MN). The control animals were maintained normothermic (37-38°C) and allowed to wake up after 36 hours of sedation and mechanical ventilation.

Data regarding the following outcome measures were collected (Table 2):

Outcome	Pre-injury	Hypothermia		Post-injury		
		Day #1	Day #2	Day #3	Day #4	Day #5
Survival						
ICP						
Neurological Score						
Behavioral Scores						
Serum Biomarkers						
Brain Histopathology						

Table 2

SOW: Task 4 (1.5 months): Data analysis and publication

The investigators have not completed this task. Data regarding rate of brain cooling, changes in vital signs, neurological deficits, rise in intracranial pressure, survival, differences in neurobehavioral test scores, brain histopathology, and serum biomarkers are being analyzed and prepared for peer-reviewed publications.

A. Justification for six-month, no-cost extension:

The investigators requested a no-cost extension of the study period from April 18, 2012 to October 18, 2012 to accomplish Tasks 1-4, for the following reasons:

1. Additional requirements from Mayo Foundation IACUC (4 months): Due to the novelty of the proposed hypothermia technology and the paucity of literature on fluid percussion injury in large animals, the Committee required the investigators to: (A) show the technology is safe and effective in four non-injured swine maintained hypothermic for 48 hours and then revived; and (B) validate the anatomical location and force necessary to induce discernible non-lethal brain injury in swine. The investigators successfully met these requirements and the IACUC released the animals for the main study.
2. Measurement of serum biomarkers of traumatic brain injury (2 months): At the behest of the Mayo Foundation IACUC and with the approval of the sponsors, the investigators have modified the protocol to include the periodic measurement of the following serum biomarkers: S-100 beta, neuron specific enolase (NSE), glial fibrillary acid protein (GFAP), and neurofilament heavy chain (NF-H). Additional time is necessary to validate the reactivity of commercially available antibodies to pig serum proteins and then perform the radioimmunoassay of the marker proteins. The measurements will be done at Mayo Immunoassay Research Laboratory in accordance with established industry standards.

- B. Preliminary survival data: Of the animals subjected to severe fluid percussion injury, 7 of the 8 hypothermic animals survived the entire duration of the study. In the control group, only 4 of the 8 survived to day #5. The cumulative survival of the animals as a function of time post-injury is shown in Figure 5. In the next few weeks, the investigators will analyze the mortality figures in light of brain histopathology, serum biomarker levels and necropsy findings.

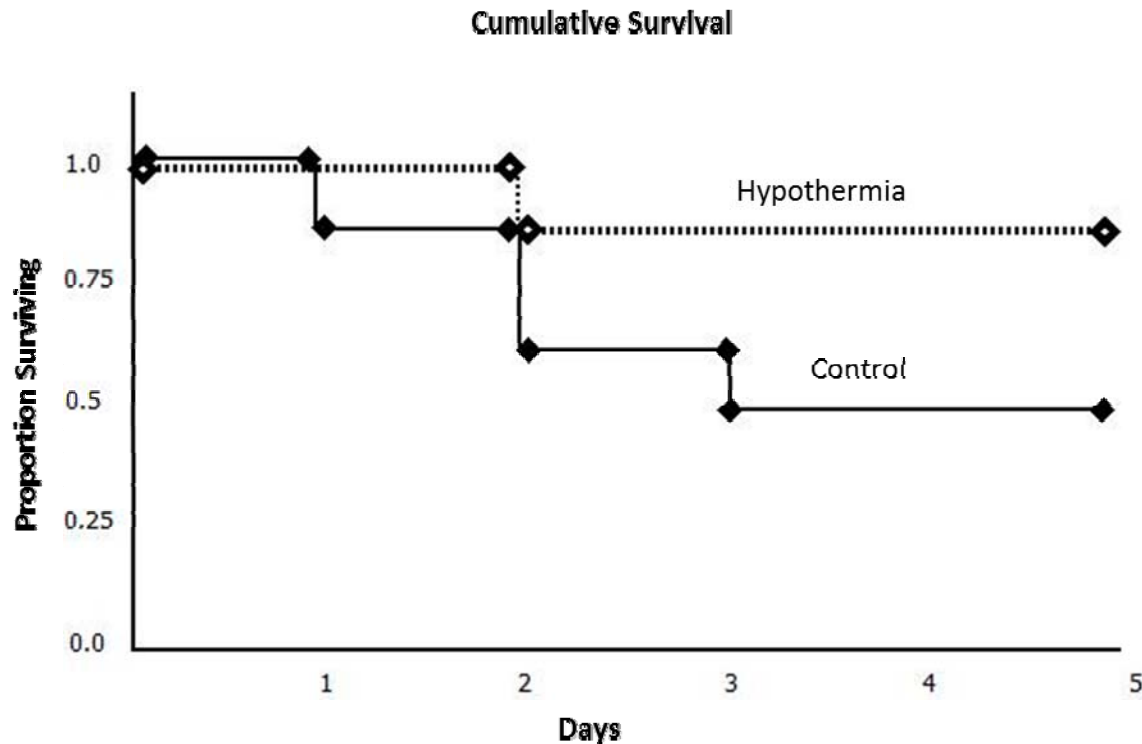


Figure 5

In all animals that failed to thrive, standard cardiopulmonary resuscitation measures, including endotracheal intubation, chest compressions, epinephrine, and defibrillation were attempted for several minutes before pronouncing death.

KEY RESEARCH ACCOMPLISHMENTS:

- Development of novel hypothermia technology – built prototype
- Confirmed the feasibility of rapid heat extraction from the lungs
- Confirmed the safety and feasibility of perfluorocarbon aerosol inhalation
- Confirmed the feasibility of prolonged maintenance of hypothermia in pigs
- Refined neurobehavioral tests for use in TBI
- Standardized the location and force of fluid percussion injury in swine
- Documented complications related to prolonged hypothermia
- Determined the predictive value of serum biomarkers following TBI
- Determined the effect of early hypothermia on ICP
- Determined the effect of early hypothermia on survival following TBI

REPORTABLE OUTCOMES:

(1). Abstract. “Rapid induction of therapeutic hypothermia through augmented heat loss from the lungs: a feasibility study in swine.” Presented at: *International Anesthesia Research Society (IARS)*, Annual Meeting, Boston, MA. May 18, 2012.

(2). 2012 Discovery Translation Program Award. Based on findings from the present study, the investigators have applied for a translational grant from Mayo Foundation. The “letter of intent” has been approved and the proposal is competitively positioned to win the award.

(3). Inventions Disclosures. The following Invention Disclosures were made to Mayo Medical Ventures: (1) “A ventilator device for inducing transpulmonary hypothermia and warming;” and (2) “Whole body cooling device for medical emergencies in the field.”

(4). Research Fellow Training. The following physicians enrolled in graduate medical education received training in large animal research: Andrew Goldberg, MD and Markos Kashiouris, MD.

CONCLUSIONS:

(1) Augmented heat extraction from the lungs using an inhalant composed of cooled heliox and perfluorocarbon aerosol is a safe and effective means to rapidly lower the brain temperature.

(2) Early initiation and rapid lowering of the brain temperature to 32-33°C (within 90 minutes) combined with prolonged maintenance hypothermia (36-48 hours) significantly improves survival in pigs following severe fluid percussion injury to the brain.

(3) Hypothermia predictably lowers intracranial pressure and prevents the secondary rise in pressure seen hours after the initial injury.

(4) Hypothermia was associated with more of the following complications: generalized edema, polyuria, hypotension, cardiac arrhythmias, hypokalemia, hyperglycemia, lactic acidosis, ileus, increased susceptibility to infection, tracheobronchial mucus plugs, coagulopathy, and decubitus ulcers.

FUTURE DIRECTIONS:

(1) The investigators request a no-cost extension of time to complete Task 4. The study has generated a large volume of new data that requires careful scrutiny and analysis before peer reviewed publication. The animal studies were completed just a few weeks ago and we are now engaged in measurements of serum biomarkers, histopathological examination of the brain, and analysis of the neurobehavioral scores. (*Please see justification under SOW Task 4.*)

(2) Add “blast injury with hemorrhage” arm to the study (6 months). The investigators would like to add a second group of hypothermic animals subjected to blast-induced TBI plus hemorrhagic shock (HS) for 60 minutes. Since TBI is rarely an isolated event, the addition of hemorrhagic shock would more closely mimic battlefield injuries. We will pursue this arm of the research in two stages:

- Stage I: Build blast tube (3 months). In collaboration with engineers with expertise in blast research, we will build a plastic explosive-driven blast tube capable of generating

blast overpressures in the range of 100-500 kPa. The advantage of the ordnance-induced blast is that it will more closely mimic battlefield explosions in creating primary, secondary and tertiary injuries. In addition, explosive-driven shock waves comprise thermal energy from the fireball, differentially powerful frequencies and electromagnetic pulse, all of which cannot be created by a compressed-air blast. Following successful bench testing, four animals will be used to study this technique in non-survival experiments. In this regard, the investigators have had preliminary discussions and obtained cost quotes from Applied Research Associates, Inc., Albuquerque, NM. Some of the elements of this task will run parallel with the Task 4 timeline: formation of the engineering team, planning the location, procurement of necessary city and law enforcement permits, etc.

- Stage II: Animal tests (3 months). In eight animals, bTBI plus HS will be induced followed by transpulmonary hypothermia. Survival, rise in intracranial pressure, neurobehavioral scores pre and post injury, serum biomarkers, and brain histopathology scores will be the target outcomes.

(3) Translation of hypothermia technology to clinical use. The investigators are pursuing Mayo Discovery Translation Award funding to quickly bring this breakthrough technology to clinical use. Each year, an estimated 3.8 million Americans are likely to benefit from hypothermia as it gains acceptance not only for the management of TBI, but also cardiac arrest, stroke and acute lung injury. Our preliminary studies show the rate of cooling to be five times faster than the current fastest, non-invasive method. The investigators are working to advance the technology to the next stage of product development within a year. By the end of 2013, the investigators will perform pharmacological and toxicological studies in swine for the following FDA applications: (1) new use for heliox and PFC and (2) either the pre-market notification (510K) or the pre-market approval (PMA) of the ventilator device.

REFERENCES:

1. Clifton, G.L., et al., *Lack of Effect of Induction of Hypothermia after Acute Brain Injury*. N Engl J Med, 2001. **344**(8): p. 556-563.
2. Polderman, K.H., *Induced hypothermia and fever control for prevention and treatment of neurological injuries*. Lancet, 2008. **371**(9628): p. 1955-69.
3. Xu, L., et al., *Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade*. J Cereb Blood Flow Metab, 2002. **22**(1): p. 21-8.
4. Wang, G.J., et al., *Mild hypothermia reduces ICAM-1 expression, neutrophil infiltration and microglia/monocyte accumulation following experimental stroke*. Neuroscience, 2002. **114**(4): p. 1081-90.
5. Clifton, G.L., et al., *Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial*. Lancet Neurol, 2011. **10**(2): p. 131-9.

6. Mooney, M.R., et al., *Therapeutic hypothermia after out-of-hospital cardiac arrest: evaluation of a regional system to increase access to cooling*. *Circulation*, 2011. **124**(2): p. 206-14.
7. Kiyatkin, E.A., *Brain temperature fluctuations during physiological and pathological conditions*. *Eur J Appl Physiol*, 2007. **101**(1): p. 3-17.
8. Brodhun, M., et al., *Immunomorphological sequelae of severe brain injury induced by fluid-percussion in juvenile pigs--effects of mild hypothermia*. *Acta Neuropathol*, 2001. **101**(5): p. 424-34.
9. Gibson, J.B., et al., *Resuscitation from severe hemorrhagic shock after traumatic brain injury using saline, shed blood, or a blood substitute*. *Shock*, 2002. **17**(3): p. 234-44.

APPENDIX:

RAPID INDUCTION OF THERAPEUTIC HYPOTHERMIA THROUGH AUGMENTED HEAT LOSS FROM THE LUNGS: A FEASIBILITY STUDY IN SWINE

Authors: Matthew Kumar, MD¹; Bekele Afessa, MD¹; John Atkinson, MD¹; Larry Johnson, BS¹; Vedha Nayagam, PhD²

Affiliation: ¹Mayo Clinic, Rochester, MN 55905; ²National Center for Space Exploration Research, NASA Glenn Research Center, Cleveland, OH 44135

Introduction: Hypothermia is gaining acceptance as an adjunct therapeutic option in the management of traumatic brain injury, strokes and cardiac arrest.¹ Yet, the current methods to induce hypothermia are slow, inefficient and cumbersome.² The authors report a novel technique of rapidly inducing hypothermia through augmented heat extraction from the lungs using perfluorocarbon (PFC) mist and cooled heliox ventilation.

Methods: Six female domestic cross-bred pigs (34-35 kg) were used in this IACUC-approved study. Following induction of anesthesia, a Camino® 4-Fr fiber-optic pressure transducer tipped catheter with thermistor was inserted 1.0 cm into the brain parenchyma through a right frontal burr hole. The core temperatures were monitored in the pulmonary artery, lower esophagus, bladder, rectum, nasopharynx and tympanum. After stabilizing the baseline respiratory parameters with room air ventilation for several minutes, ventilation was switched to cooled heliox (0±2°C, He 70%:O₂ 30%) and 0.14% (v/v) PFC mist. Heliox-PFC ventilation was continued for 90 minutes or until the target temperature of 32°C was reached. All temperatures, intracranial pressure, and cerebral perfusion pressure were recorded as a function of time using a data acquisition system (~0.017 Hz or faster).

Results: Core temperatures declined rapidly in all animals following the initiation of heliox-PFC mist ventilation. The brain temperatures lagged 5-7 minutes before starting to decline. The esophageal temperature (mean ±SD) reached target in 40±6.8 minutes. The brain temperature declined to target in 65±10.4 minutes (Figure 1). Cardiopulmonary functions and intracranial (5-20 torr) and cerebral perfusion (50-70 torr) pressures remained stable.

Discussion: A novel, minimally-invasive and effective technique to rapidly induce hypothermia is described. The combined influence of the thermal conductivity of helium and the vaporization of PFC produce rapid cooling of the alveolar gases. The thin alveolar membrane and the large surface area of contact between the inspired gases and the pulmonary capillary blood results in a high rate of heat transfer which rapidly cools the pulmonary blood. The subsequent flow of the cooled arterial blood to the brain reduces the brain temperature. The time lag between the core and the brain temperatures depends on the blood perfusion rate to the brain (convective flow velocity and volume). Due to the thermal mass of the blood, the brain continues to cool for several minutes after the cessation of heliox-PFC ventilation.

References:

1. Crit Care Med. 39(5):1113-1125, May 2011.
2. Crit Care. 2007; 11(4): R91.

Supported in part by US Army CCCRP W81XWH

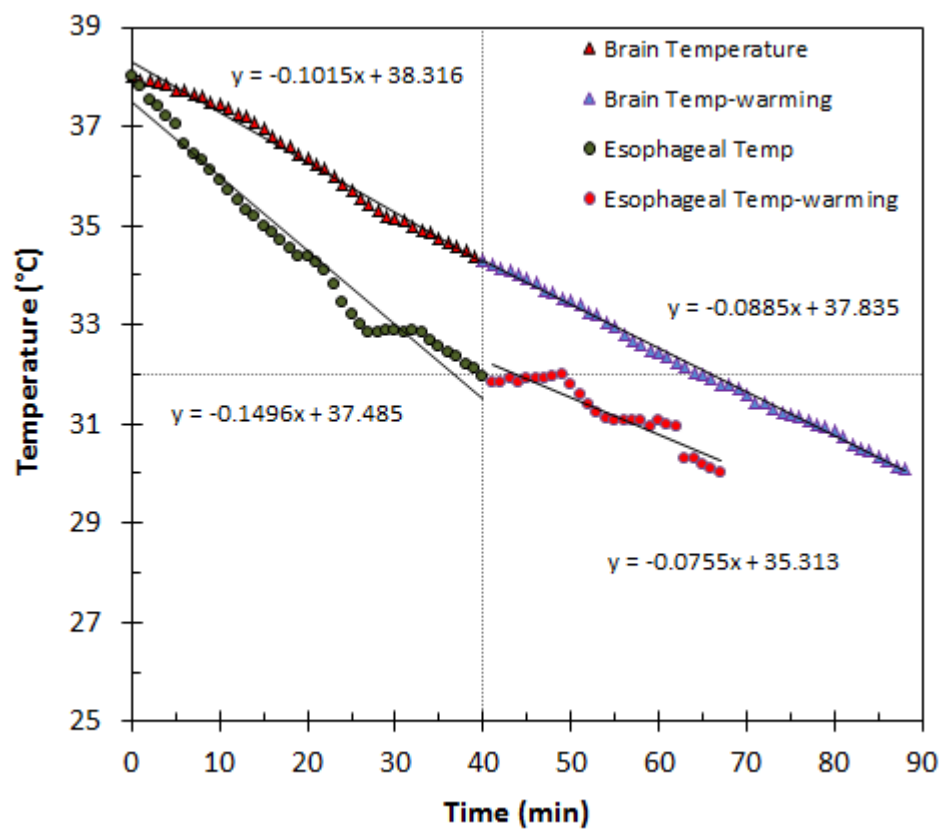


Figure 1

Presented at: *International Anesthesia Research Society (IARS)*, Annual Meeting, Boston, MA., May 18, 2012.