Potential Use of Selective Aortic Arch Perfusion (SAAP) to Induce Profound Hypothermia for Emergency Preservation and Resuscitation (EPR)

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FINAL REPORT

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DECLARATION OF INTEREST

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POTENTIAL USE OF SELECTIVE AORTIC ARCH PERFUSION (SAAP) TO INDUCE PROFOUND HYPOTHERMIA FOR EMERGENCY PRESERVATION AND RESUSCITATION (EPR) HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION IN ACCORDANCE WITH ASSIGNED DISTRIBUTION STATEMENT.

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14. ABSTRACT
The majority of potentially survivable injuries on the battlefield are associated with hemorrhage. Emergency preservation and resuscitation (EPR) is a method of extending the window of organ viability following severe hemorrhage to allow for surgical interventions and repair. Highly invasive methodologies are currently used for induction of EPR. The purpose of this study was to determine if EPR by profound hypothermia could effectively be induced by the introduction of cold fluids through the Selective Aortic Arch Perfusion (SAAP) catheter. The SAAP catheter is a balloon tipped catheter with a large lumen designed to deliver high volumes of fluids directly to the aortic arch while facilitating hemostasis similar to resuscitative endovascular balloon occlusion of the AORTA (REBOA). A swine model of hemorrhage induced cardiac arrest was used. Results show that the SAAP catheter was able to effectively induce EPR, defined by brain temperature, in only one subject out of the ten tested. These results indicate that induction of EPR through the SAAP catheter is possible, but unlikely.

15. SUBJECT TERMS
Hemorrhage, Traumatic Cardiac Arrest, Selective Aortic Arch Perfusion, Emergency Preservation and Resuscitation, Trauma

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1.0 SUMMARY

Emergency preservation and resuscitation (EPR) is a method of extending the window of organ viability and increasing patient survival following hemorrhage-induced traumatic cardiopulmonary arrest (HiTCA). This extra time allows for surgical interventions to repair life-threatening injuries and attain hemostasis. Various methods have been utilized to achieve EPR, including the use of hydrogen sulfide gas and induction of profound hypothermia (<15°C core temperature). For induction of hypothermia, researchers typically use a thoracotomy with inserted through the aortic laceration to introduce a catheter for rapid cooling. The invasive nature of these interventions is not practical in an emergency setting. A recent advancement in treatment of HiTCA is the utilization of Selective Aortic Arch Perfusion (SAAP), which employs a balloon-tipped catheter to deliver resuscitation fluids directly to the aortic arch and coronary arteries while temporarily occluding distal vessels. The minimally invasive nature of this technique would make it preferable to other hypothermic interventions. The purpose of this study was to determine if profound hypothermia could effectively be induced through an introduction of cold fluids using the SAAP catheter.

Yorkshire swine (40-60 kg) were anesthetized, instrumented, and underwent splenectomy. Two methods were utilized to induce HiTCA: a hybrid model using laparoscopic liver injury with controlled hemorrhage or controlled hemorrhage alone. HiTCA was defined in both groups as a carotid systolic blood pressure <10mmHg. After a three-minute arrest period, the SAAP balloon was inflated, and cold saline (~6° C) was infused through the SAAP catheter at 750 mL/min. After an initial volume of cold saline (4-5L) was infused, blood was drained from a previously placed external jugular catheter and recycled into the cooling circuit. A liver repair was performed after 15 minutes of hypothermia induction in the hybrid injury group. Subjects that achieved hypothermia were rewarmed to physiologic temperature using autotransfusion as well as blood from a donor pool. Core temperature was measured rectally, heart temperature measured by pulmonary artery catheter, and brain temperature measured by a temperature probe implanted through a burr hole into the brain. The primary outcome of this study was the rate of brain cooling. Secondary outcomes were survival, return of spontaneous circulation (ROSC), hemodynamics, and a rate of rewarming comparison between current groups and those from previous studies.

Data produced across ten subjects exhibited an average cardiac cooling rate of 0.87°C/min over the first 25 minutes, and an average brain cooling rate of 0.39°C/min over the first 25 minutes, significantly slower than the desired 2°C/min achieved in previous studies. Only one subject out of all subjects tested reached the desired rate of 2°C/min.

Preliminary data suggests that the SAAP catheter may be ineffective for rapidly inducing profound hypothermia without significant improvements and adjustments. Further investigation is necessary to optimize this technique as well as other effective means of implementing EPR.

2.0 INTRODUCTION

Hemorrhage is associated with most potentially survivable deaths occurring on the battlefield.[1] This is often due to uncontrolled hemorrhage causing hemorrhage-induced traumatic cardiac arrest (HiTCA). Emergency Preservation and Resuscitation (EPR) is the process by which patients are induced into a state that preserves tissue to prevent further damage. The approach is being principally developed for patients who have undergone cardiac arrest and need extra time for treatment or transport. This technique is particularly well-suited for HiTCA from battlefield injuries.

Two methods have been utilized to induce EPR: chemical and temperature. Chemically induced EPR is achieved using hydrogen sulfide (H_2S).[2, 3] H_2S induces a state of preservation though inhibition of cellular respiration. Inhibition occurs by reversibly binding to cytochrome c oxidase, thereby blocking the electron transport chain. Studies using rodent and swine models have shown that inhalation of H_2S can be used to induce a reversible preservation-like state.[2] Unfortunately, H_2S is not only highly flammable but poisonous due to its inhibition of cellular respiration leading to reservations of using it as a therapeutic. Other compounds with similar inhibition of cellular respiration include carbon monoxide, nitric oxide, and hydrogen selenide, but have not been widely studied for their use in EPR.[4]

Decreasing body temperature (induced hypothermia) to slow metabolism is a well-supported and frequently used clinical method. Perhaps the best known and well-studied example of hypothermia decreasing metabolism comes from examples of hibernation where rodents decrease their body temperature to near freezing to minimize metabolism.[5] Other examples come from accidents occurring in freezing temperatures which have led to patients surviving following drownings or cardiac arrest. A recent example comes from a British woman who completely recovered after a six-hour cardiac arrest while hiking in freezing weather.[6] Finally, the most prominent example of clinical use of hypothermia is the routine storage of organs harvested for transplantation in refrigerated containers to extend their viability.

Hypothermia can be separated into mild (33-36°C), moderate (28-32°C), deep (18-28°C), profound (10-17°C), and ultraprofound (<10°C) categories. Mild hypothermia is most often used clinically following cardiac arrest as a therapy termed "targeted temperature management" (TTM).[7, 8] Mild hypothermia is achieved through various means including surface cooling, infusion of cooled fluids, and through the use of intravascular cooling balloons.[9] Moderate and deep hypothermia are used for cardiothoracic surgeries including aortic arch repair.[10] Cooling for these temperatures is accomplished using cardiopulmonary bypass (CPB) machinery to directly infuse cold fluids to the body. More advanced cardiothoracic surgeries including heart repair and heart transplant require profound hypothermia. Similar to moderate and deep hypothermia, profound hypothermia is performed utilizing CPB equipment. Finally, although EPR requires a state of profound hypothermia, special considerations should be taken into account with regard to rate, length, and type of techniques for induction when severe injuries have been incurred.

2.1 Animal Studies

Past studies utilizing animal models have provided valuable information on the potential utilization of EPR for severely injured patients. Rats, rabbits, dogs, and pigs have all been utilized to characterize the critical aspects and methods for effective EPR.[11-19] These studies have narrowed the range of possible temperatures, rate of temperature changes, fluids utilized, and methods used for induction.

The rate of cooling, target temperature, and rate of warming are all critical for obtaining good neurological and physiological outcomes following EPR. A fast rate of cooling has been shown to be optimal. In one set of experiments, Alam et al. showed that the subjects cooled at a rate of 2°C/min had the highest rate of

survival compared to those cooled at 1°C/min or 0.5°C/min.[20] Temperatures ≤ 15° appear to be necessary for effective EPR with 10° showing the least negative complications.[19, 21] Additionally, one study demonstrated that 10°C was superior to 5°C with regard to survival and neurologic outcome.[22] Rewarming rate is also critical: 0.5°C/min is superior to 1°C/min or 0.25°C/min rewarming.[23] Finally, length of profound hypothermia with good outcomes has ranged between 60 minutes at 10°C in a swine model of hemorrhagic shock to 90 min at 15°C in a normovolemic swine model.[19, 24]

Various methods have been used to induce profound hypothermia for EPR. Nearly every method utilized is a form of CPB. One particularly common method is to induce CPB, and thereby EPR, by direct cannulation of the aortic arch following a thoracotomy with venous catheters placed directly into the right atrium.[17, 20] Less invasive methods have utilized large bore catheters (14 -20 Fr) placed in the femoral artery/vein or a carotid artery/jugular vein to induce EPR.[19] Other groups have used modified or custom-made catheters. For example, Janata et al., modified a 12 Fr Foley catheter in order to allow sufficient flow rates into the aortic arch.[18] Weiser et. al. used a 16Fr Aortic Flush Balloon Catheter to rapidly perfuse cold saline for induction of EPR for management of cardiac arrest induced via ventricular fibrillations.[25]

The fluids used to induce profound hypothermia for EPR appear to be critical for recovery and good neurological outcomes. Many of the original studies and some more recent ones have used simple crystalloids for induction.[16, 21] Other studies have added various factors to crystalloids to improve EPR. For example, addition of glucose and oxygen to saline improved both survival and neurologic scores in a canine model.[26] Many studies have used an "intracellular" fluid that mimics the environment inside cells during profound hypothermia. One study showed a new intracellular solution improved neurologic outcomes in dogs when compared to a crystalloid control.[27]

2.2 Human Trials

A clinical trial is currently being carried out in Baltimore, Maryland by Sam Tisherman under the title: Emergency Preservation and Resuscitation for Cardiac Arrest From Trauma.[28] In this trial, once the standard hemostatic and resuscitative therapies are shown to be ineffective, the patient is enrolled into the trial. Trial patients will receive ice cold saline introduced into the thoracic aorta to induce profound hypothermia. Following surgical repair, the patient will then be rewarmed and further treated as appropriate.

2.3 Selective Aortic Arch Perfusion

Selective Aortic Arch Perfusion (SAAP) is a technique where a balloon-tipped catheter containing a large central lumen is placed into the aortic arch through the femoral artery. The SAAP catheter is capable of delivering fluids rapidly to the brain, heart, and lungs while occluding the descending aorta. This occlusion of the aorta works similar to zone 1 REBOA (Resuscitative Endovascular Occlusion of the Aorta) to help treat non-compressible torso hemorrhage (NCTH). SAAP has been shown to be useful for treating medical cardiac arrest due to ventricular fibrillations and hemorrhage-induced traumatic cardiac arrest.[29-31] The SAAP catheter is commercially available as an experimental device from Resusitech Inc (Menlo Park, CA). The device is currently undergoing review for FDA approval.

The goal of this study was to utilize the SAAP catheter to induce profound hypothermia. Utilization of the SAAP catheter would provide a less technically challenging method for inducing EPR. Furthermore, the SAAP catheter is an adjunct for hemorrhage control similar to REBOA and can be used to treat cardiac arrest depending on the patient and circumstances.

3.0 METHODS

The experimental protocol was approved by the 59th Medical Wing Institutional Animal Care and Use Committee (IACUC). Experiments were performed at the 59th Medical Wing, United States Air Force, Office of the Chief Scientist, in a facility accredited by the American Association for the Accreditation of Laboratory Animal Care and conducted in accordance with guidelines established by the Public Health Service Policy on Humane Care and Use of Laboratory Animals and Office of Laboratory Animal Welfare. The procedures were performed by qualified personnel under the supervision of on-site veterinarians.

3.1 Injury Model

The liver injury model employed in this study was based on a previously published protocol describing the use of laparoscopic liver injury in conjunction with a controlled arterial hemorrhage to yield a model of hemorrhage-induced traumatic cardiac arrest (HiTCA), defined as a systolic blood pressure (SBP) ≤10mmHg for greater than ten seconds.[29] This model has been previously used to compare the efficacy of SAAP versus REBOA for reversing cardiac arrest. In order to evaluate the ability of SAAP to rapidly induce profound hypothermia as a means of EPR that extends the window of organ viability following HiTCA, we employed this model as shown in the experimental design (Figure 1). Sixty minutes of cardiac arrest in a state of profound hypothermia was chosen based on results from previous studies identifying 60 minutes as the upper limit for cardiac arrest without neurological damage.[24]

3.2 Blood Transfusion

Up to three units of whole blood (450mL per unit) was collected and measured by weight from each animal during the controlled arterial hemorrhage for autotranfusion or as part of a donor pool for use in a later experiment. Whole blood was collected via the right common femoral artery and stored in citrated (CPD-1) blood donation bags (TERUFLEX, Terumo Corp. Tokyo, Japan). The total volume of each unit with anticoagulant was 500mL. Blood was kept at 37°C for autotranfusion during rewarming.

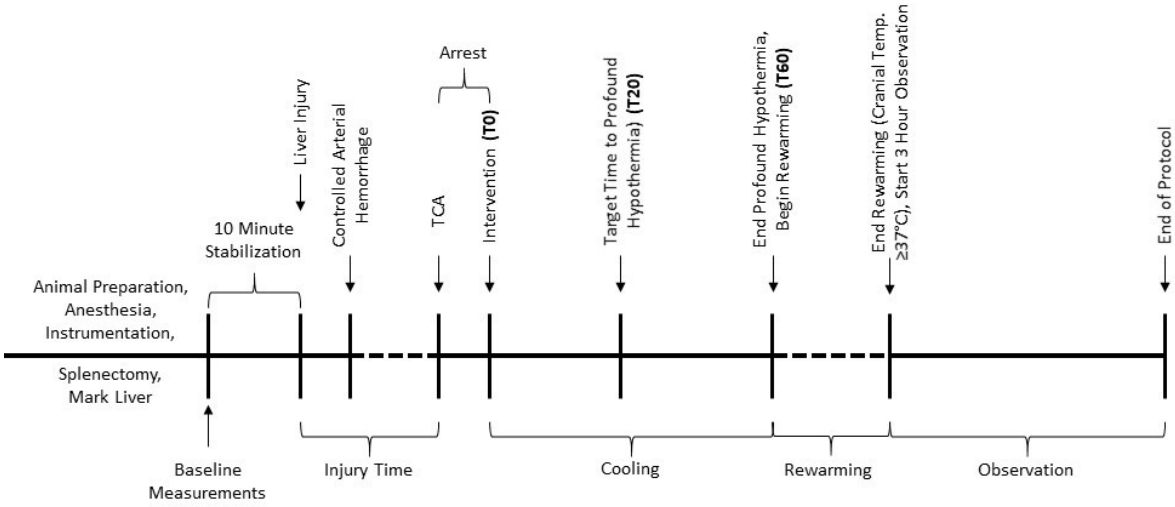

Figure 1. Protocol Timeline
At start of intervention, the SAAP (selective aortic arch perfusion) balloon was inflated and then immediately followed with a rapid 50mL bolus of Lactated Ringer's solution. If subject did not reach target temperature within twenty minutes, cooling continued until T60 then experiment discontinued. If assigned to no liver in jury group, controlled arterial hemorrhage started immediately after 10-minute stabilization. Experiment discontinued if subject met death criteria (Mean Arterial Pressure < 20mmHg and $EtCO_2$ < 15mmHg) at any point during protocol. TCA; Traumatic Cardiac Arrest.

3.3 Animals

Male Yorkshire Landrace cross swine (*Sus scrofa,* 40-60kg) were obtained from a single local, USDA-licensed vendor. The original protocol was written to use 70-90kg swine, due to their anatomical and physiological resemblance to the average American warfighter. However, this weight range was then changed to 40-60kg as the SAAP catheter was more appropriately sized for swine in this weight range due to its ability to reach the aortic arch from insertion in the femoral artery. Animals were housed and fed in 59th Medical Wing facilities in accordance with operating instructions governing animal housing (40V-013-Feeding and Watering Schedules and 40V-014-Quarantine and Stabilization of Animals). Animals were allowed to acclimate to the facility for at least 7 days prior to surgery with free access to food and water. Feed was withheld 12 hours prior to surgery to reduce the likelihood of aspiration during intubation and anesthesia. The "no liver injury" group was included as a control for potential decreased rate of brain cooling due to lost cold fluid volume to the intraperitoneal space via continued retrograde liver hemorrhage beyond initiation of TCA.

3.4 Anesthesia and Instrumentation

Animals were sedated via an intramuscular injection of Telazol (4.4mg/kg) and subcutaneous Ketamine (2.2mg/kg). An intramuscular injection of Buprenex (0.01mg/kg) was also given as pre-emptive analgesia. Animals were intubated endotracheally using a laryngoscope and a cuffed endotracheal tube was held in position by roll gauze. Placement was confirmed by auscultation over both lung fields and mid-epigastrium, as well as assessment of $ETCO_2$ waveform. Anesthesia was induced via mask with 2-4% isofluorance, weaned down to 1-2.5% during the protocol to maintain a Mean Alveolar Concentration (MAC) of 1.2-2.0. Fraction of inspired oxygen (FiO_2) was set between 40 and 60%, and slowly weaned to 21% (atmospheric air) by the start of the 10-minute stabilization period. At the start of treatment intervention, FiO_2 was increased to 1.0, as would be done in clinical management. The $EtCO_2$ was kept between 35 and 45mmHg

until the 10-minute stabilization, maintained with an initial tidal volume of 7-10mL/kg and adjusted as needed. Once cardiac arrest was initiated, ventilator settings were not adjusted unless a return of spontaneous circulation (ROSC) was observed so that $ETCO_2$ could be used as a surrogate variable for cardiac output (CO). Animal temperature was maintained between 37°C and 39°C using heating adjuncts as needed until discontinued at initiation of TCA.

When anesthetized, electrocardiography, physiological monitoring, blood sampling, and vascular access instrumentation were prepared. Percutaneous blood sampling and vascular access lines were placed using ultrasound guidance. The following sites were cannulated with an 8.5Fr catheter: 1) right carotid artery for intra-aortic blood pressure (BP) monitoring via a micromanometer-tipped catheter (Millar Inc. Houston, TX USA) as well as blood sampling; 2) right external jugular vein for pulmonary artery BP, cardiac output, mixed venous oxygen saturation (SvO_2), and cardiac temperature monitoring via a Swan-Ganz thermodilution catheter (Edwards Lifesciences, Irvine, CA USA); 3) left external jugular vein for fluid infusion/exsanguination. A 12Fr catheter was placed percutaneously in the right common femoral artery for controlled arterial hemorrhage and insertion of the SAAP balloon catheter. The SAAP catheter is shown in Figure 2.

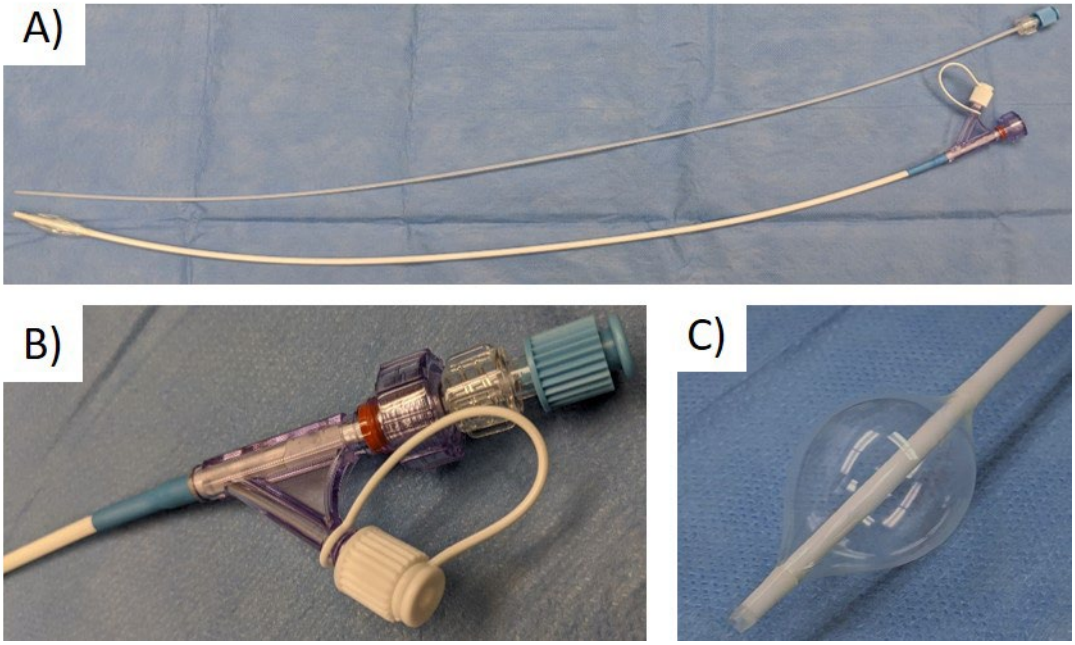

Figure 2. SAAP Balloon Catheter
A) The SAAP catheter is shown below its obturator, used to occlude the inner lumen of the catheter until removed. The catheter runs 54 cm long with a 9 Fr internal lumen. It can be introduced through a 12 Fr introducer sheath into the femoral artery and requires a guide wire for placement. **B)** The distal end of the catheter consists of two ports: a side port for inflating the balloon, and the other for perfusing fluids through the central lumen. **C)** The balloon has a 20 mL inflation volume. The proximal tip is flexible to prevent scraping of the arterial wall during insertion.

A midline cut down to the left carotid artery was undertaken to place a transonic flow probe (Transonic Systems Inc., Ithaca, NY USA) to measure the rate of blood flow to the brain. Cerebral temperature was measured via a T-Type Implantable Thermocouple Probe (ADInstruments, Colorado Springs, CO USA) inserted through a cranial burr hole. Rectal temperature was monitored via a rectal temperature probe that was inserted during initial animal preparation. A disposable peripheral capillary oxygen saturation (SpO_2) monitor was placed on the front right hoof.

3.5 Surgery

Following line placement and instrumentation, a splenectomy was performed via a midline laparotomy. The *Sus scrofa* spleen is contractile and provides autotranfusion following injury that may limit the translatability of the results to clinical practice.[32] After the spleen was removed, the left medial liver lobe was retracted, and the left-lateral lobe was marked along the projected line of transection using electrocautery, then returned to its anatomical position. Four trocars for laparoscopic surgery were placed as follows: a 10/12mm trocar placed just cephalad and left of the urethral opening, two 10/12mm port trocars placed lateral to the third and fourth nipple interspace of their respective sides, and a 5mm working port trocar placed medial to the right third and fourth nipple interspace. Additionally, a direct cystostomy was performed and a Foley catheter was placed in order to prevent the physiological effects of a distended urinary bladder during the protocol. The peritoneum and anterior abdominal wall were closed, followed by observation of a ten-minute stabilization period.

3.6 Hybrid Liver Injury and Controlled Hemorrhage

After the ten-minute stabilization period, the subject was allocated to either the liver injury group or no liver injury group. If in the hybrid liver injury group, the abdomen was insufflated via laparoscopic port to a pressure of 12 mmHg. The left lateral lobe of the liver was excised with 5mm Metzenbaum endoshears along the line marked during the laparotomy, yielding an approximately 70% transection. After two minutes, or when the injury was completed, the abdomen was rapidly desufflated, instruments and ports were removed, and the laparoscopic holes were approximated with skin staples. After five minutes of free liver bleeding, a controlled arterial hemorrhage was initiated at 3mL/kg/min via the femoral artery using a Masterflex peristaltic pump and tubing (Cole-Parmer, Vernon Hills, IL USA). Hemorrhage was continued until the time of arrest (onset of TCA, SBP < 10mmHg for > 10 seconds). The hemorrhage was discontinued, and a three-minute arrest period was observed.

If the subject was allocated to the no liver injury group, the liver was left intact, and the controlled arterial hemorrhage was initiated immediately following the ten-minute stabilization. The hemorrhage rate started at 3mL/kg/min but was adjusted as needed to prevent circulatory collapse. At the time of arrest (onset of TCA, SBP < 10mmHg for > 10 seconds), the hemorrhage was discontinued, followed by a three-minute arrest period as with the hybrid liver injury. The total hemorrhage volume was determined by weight immediately after TCA was achieved. If the hemorrhage volume exceeded the three units collected for autotransfusion/ donor blood, blood was fed into an empty and tared surgical bowl for measurement.

3.7 Intervention

Three minutes after the onset of TCA, the SAAP balloon catheter was advanced to the distal aortic arch, with the balloon just superior to the diaphragm. Balloon placement was confirmed via fluoroscopy and then inflated with 12mL of injectable contrast diluted 50% with sterile water. A 50mL bolus of Lactated Ringer's solution was rapidly flushed through the SAAP catheter to close the aortic valve, followed by continuous infusion of cold (6°C) normal saline at a rate of 750mL/min (defined as T0). The fluid temperature was chosen based on the desired brain temperature cooling rate (2°C/min) determined by previous studies and

maintained with a heater cooler set at 2°C.[20] The circuit for cold fluid infusion/ exsanguination is shown in Figure 3.

After infusion of approximately 4L of normal saline, the line leading from the left external jugular vein was opened to allow exsanguination of warm blood/saline mixture from the subject. Once sufficiently diluted with cold saline, this line was opened to the Belmont reservoir, completing the circuit. Chilled normal saline was added to the reservoir as needed to maintain > 500mL of fluid in the circuit at all times.

Brain and pulmonary artery temperatures were continuously monitored with a goal of reaching a brain temperature of ≤15°C within twenty minutes from the start of fluid infusion. Cooling was maintained for up to sixty minutes post-intervention. If the target brain temperature was not reached within twenty minutes, the cooling induction continued for forty additional minutes without any attempt of rewarming. When the subject reached the target brain temperature, rewarming commenced at the end of the cooling period, with a target warming rate of 0.5°C/min. Fresh whole blood (37°C) was gradually introduced to the circuit while continuing to exsanguinate cold saline. The temperature of the heater-cooler was gradually increased to control the warming rate. If the subject never reached target brain temperature, we stopped experimental procedures at sixty minutes.

Once normal physiologic temperature (37°C) was reached, a three-hour observation was started. If return of spontaneous circulation (ROSC) was not achieved, three countershocks were given in an attempt to restore circulatory rhythm. If ROSC was still not achieved, rewarming/observation were discontinued, and the subject was euthanized. If the subject met the pre-determined death criteria for > 2 minutes at any point during the experiment, the experiment was discontinued, and the subject was euthanized.

3.8 Protocol Definitions and End Points

Traumatic cardiac arrest (TCA) was defined as SBP < 10mmHg for > 10 seconds. Return of spontaneous circulation (ROSC) was defined as SBP > 90mmHg after the start of intervention (T0). Qualification for death criteria was determined to be a MAP < 20mmHg and an $ETCO_2$ < 15mmHg sustained for more than 2 minutes. These criteria qualified the subject for euthanasia and cessation of the protocol. Additional criteria for euthanasia included failure to reach the target brain temperature (≤15°C) within sixty minutes from the start of treatment, or the absence of ROSC during/after rewarming and administration of 3 countershocks (biphasic 160 J).

Profound hypothermia was defined as a brain temperature ≤15°C. The desired cooling rate was defined as a decrease in brain temperature of ≥2°C.minute, and the desired rate of rewarming was defined as an increase in brain temperature of approximately 0.5°C/minute. These values were chosen based on previous reports using emergency preservation and resuscitation methods.[20, 23]

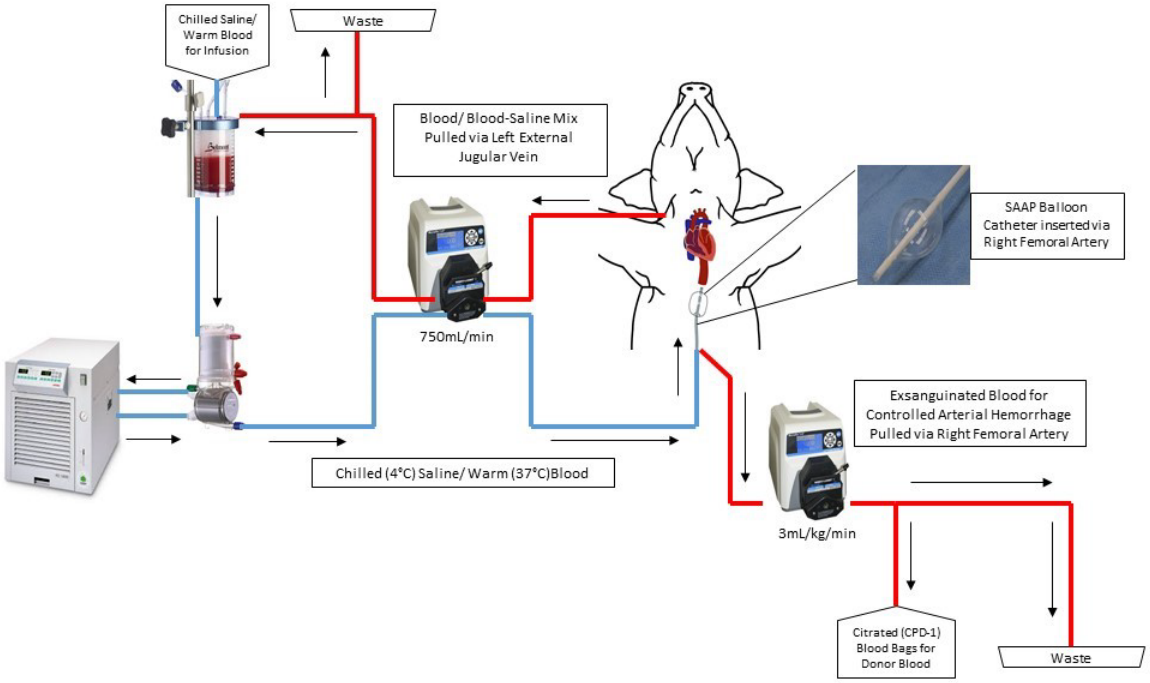

Figure 3. Experimental Cardiopulmonary Bypass Circuit.
Prior to intervention, the circuit was primed with 1L of cold (6°C) normal saline. The heater cooler circulated sterile water at 2°C through an oxygenator for heat-exchange to control the temperature of fluid flowing through the circuit. Controlled arterial hemorrhage was performed via the same line used for SAAP insertion and fluid infusion (right common femoral artery). Up to 4L of normal saline was infused prior to exsanguination via the left external jugular vein. Warm blood was exsanguinated to waste until sufficiently drained, at which point the circuit was opened to the Belmont reservoir for recirculation. The following equipment was utilized in the circuit: 1) Heater Cooler (Julabo USA Inc., Allentown, PA USA); 2) Belmont 3 Liter Reservoir (Belmont Medical Technologies, Billerica, MA USA); 3) Affinity NT Oxygenator (Medtronic Inc. Minneapolis, MN USA); 4) Masterflex L/S Standard Digital Pump (Cole-Parmer, Vernon Hills, IL USA); 5) Masterflex Tygon E-LFL Pump Tubing, L/S 25, 16 (Cole-Parmer, Vernon Hills, IL).

3.9 Post Experimental Procedures

At the end of the protocol, subjects were euthanized by a trained laboratory technician with an intravenous (IV) injection of Pentobarbital (100mg/kg) in accordance with the American Veterinary Medical Association euthanasia guidelines. Cessation of vital signs was confirmed via auscultation of the lungs and heart. The abdomen was reopened for gross examination of any excess fluid buildup within the intraperitoneal space. The liver was examined to accurately describe the extent of the liver injury.

3.10 Data Acquisition

A PowerLab data acquisition system (ADInstruments, Colorado Springs, CO USA) was used to record data points for intra-aortic arch BP using a Millar micromanometer-tipped pressure catheter. This data was also used to calculate systolic, diastolic, and mean arterial pressures. These values were recorded as mean values every five seconds. This system also recorded live intracranial temperature readings using a T-Type Implantable Thermocouple Probe, carotid blood flow via a transonic flow probe, and pulmonary arterial BP from the Swan-Ganz catheter. Other variables were recorded or calculated at 60-second intervals (heart rate; $ETCO_2$; central venous pressure [CVP]; peripheral capillary oxygen saturation [SpO_2]; systolic, diastolic, and mean pulmonary arterial pressures; continuous cardiac output [CCO]; mixed venous oxygen saturation [SVO_2]; rectal temperature; and cardiac temperature).

Arterial blood samples (~1mL) were collected from the right carotid artery at the following time points: prior to splenectomy (baseline 1), following splenectomy (baseline 2), at TCA, at a brain temperature of 15°C, at the end of 60 minutes of profound hypothermia (T60), after rewarming to 37°C, and every 30 minutes after reaching 37°C for blood gas analysis (12 total). Arterial blood samples (~20mL) were collected from the right carotid artery at the following time points: following splenectomy (baseline 2), at the end of 60 minutes of profound hypothermia (T60), after rewarming to 37°C, one hour after reaching 37°C, and at the end of observation.

3.11 Outcomes

The primary outcome of this study was the ability to reach profound hypothermia (intracranial temperature ≤15°C) at a rate ≥2°C cooling per minute.

Secondary outcomes of this study included carotid blood flow to the brain and survival (determined by ROSC). For any subjects that achieved ROSC, physiological and metabolic parameters (arterial blood gas, HR, BP, and blood chemistries) were assessed at the end of the observation. Furthermore, neurological damage was assessed via histopathological analysis of hippocampus tissue sections.

3.12 Data Analysis

Data is presented as mean ± standard deviation for continuous variable or by percent for categorical variables. Overall rates of cooling were determined by the slope of the trend line for temperatures over the first 25 minutes of cooling. Goodness of fit was determined using R^2 value of the trend line. Significance was assessed by Student's t-test. All statistics were performed using Microsoft Excel 2013.

4.0 MAJOR EVENTS/MILESTONES/SUCCESSES

- FY17Q2 – Obtained IACUC approval received for Phase I

- FY18Q4 – Heater cooler received.
- FY19Q1 – Data acquisition systems received.
- FY19Q1 – Phase I experimental matrix initiated.
- FY19Q3 – Phase I experimental procedures complete
- FY19Q4 – Phase II protocol was conditionally approved by the IACUC. Supplies were ordered; however, we were unable to start procedures before money expiration.

5.0 RISK ASSESSMENT

5.1 Risk Analysis

Scheduling delays during the project:

- Significant delay in acquisition of heater/cooler system of ~22 months
- Significant delay in acquisition of data acquisition system of ~24 months
- Delay in contract technician of ~18 months
- Impact of delays: inability to complete project as originally proposed.

5.2 Technical Challenges

The objective of this project was to develop and evaluate a new method of inducing profound hypothermia to be used on patients undergoing HiTCA. Simultaneously, the new method would need to provide hemostatic support and able to be undertaken quickly. These factors provide for a technically challenging but high advancement in warfighter trauma care.

6.0 TRANSITION PLAN

6.1 Military Relevance

During OIF/OEF, NCTH accounted for the greatest number of potentially survivable combat deaths. There is currently no effective management of NCTH and its' ultimate manifestation - HiTCA. Approximately 90% of NCTH combat deaths occur before arrival at a medical treatment facility (i.e., pre-hospital) and there was no statistical improvement in this mortality rate over OEF (a stark contrast to other conditions over this period). This project was meant to advance the understanding HiTCA and NCTH management in the pre-hospital setting and develop a technology that would result in substantial improvements in combat survival by use of EPR in different scenarios.

This effort was designed to address the most common cause of potentially survivable prehospital deaths on the battlefield: NCTH. Additionally, this effort addressed the current capability gap of EPR for patient transport to higher echelons of care. This project specifically addressed the 2015 AFMS ICL RTK #4 gap "Lack the feasibility and practicability of Emergency Preservation and Resuscitation (EPR) (suspended animation) for patient transport."

6.2 Transition Strategy

This project aimed to determine the ability to easily and rapidly induce profound hypothermia for use in emergency preservation and resuscitation. Additionally, optimal solution and equipment was analyzed and compared for inclusion of a field-ready toolkit. The phase completed for this project resulted in a scientific paper to share knowledge with the scientific and military end user communities. Additionally, the information gained through these experiments will be further presented at scientific conferences to facilitate

knowledge dissemination. Air Mobility Command and SG5 Knowledge Product Team will be consulted for guidance on knowledge transition path for Phase I completed data.

7.0 RESULTS

7.1 Baseline Values

Nineteen subjects were enrolled in this study. Nine were utilized as protocol development subjects in order to optimize this novel model. The remaining ten subjects were split between two groups with five subjects per group: with liver injury and without liver injury. Baseline values were similar with no significant differences between groups (Table 1). Overall, the subjects weighed 47.6 ± 6.7.

Table 1. Baseline values

	Controlled	Hybrid	*p*-value
n	5	5	-
Male (%)	5/5 (100%)	5/5 (100%)	0.999
Weight (kg)	44.5 ± 3.9	51.5 ± 7.9	0.124
Length (cm)	146 ± 8	151 ± 6	0.410
Spleen (kg)	350 ± 41	376 ± 52	0.395
pH	7.49 ± 0.03	7.50 ± 0.06	0.767
Potassium (mmol/L)	4.4 ± 0.74	3.8 ± 0.6	0.206
Lactate (mmol/L)	2.7 ± 1.6	2.4 ± 1.0	0.730
Base excess (mmol/L)	4.1 ± 3.9	6.7 ± 3.0	0.262
Hemoglobin g/dL	9.9 ± 1.5	9.9 ± 1.0	0.962

7.2 Hypothermia induction

Temperatures were recorded from brain, heart (using the Swan-Ganz catheter), and rectum in order to measure temperature changes during induction of hypothermia and during rewarming if the subject achieved profound hypothermia. Figure 4 shows the progression overtime of the rectal temperatures. Overall, the subject's baseline temperatures were 37.3 ± 0.6. By the end of the cooling period, rectal temperatures had decreased to an overall temperature of 36.6 ± 1.4°C. These differences were not significantly different (p=0.20) and did not represent a meaningful decrease in temperature.

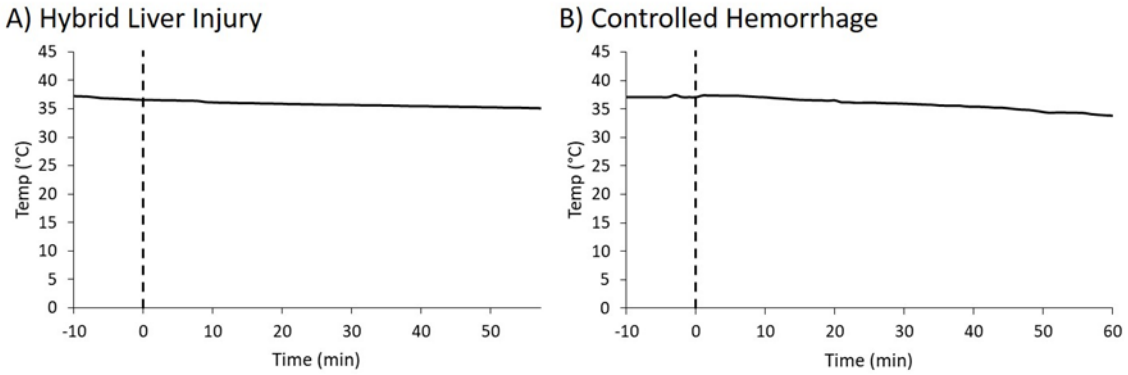

Figure 4. Rectal Temperatures.
A) Hybrid liver injury **B)** Controlled hemorrhage injury. Dashed line represents initiation of hypothermia induction (t=0)

Figure 5 shows the measured temperatures of the pulmonary artery using the Swan-Ganz catheter. Individual subjects are shown in A and B for both groups, while mean temperatures along with associated trendline are shown in C and D. The rate of cooling for the entire group is shown as the slope of the trendline. Overall pulmonary temperature was 37.7 ± 1.0°C and was not significantly different between groups. Variability was much greater in the hybrid liver injury group compared to the controlled hemorrhage group only.

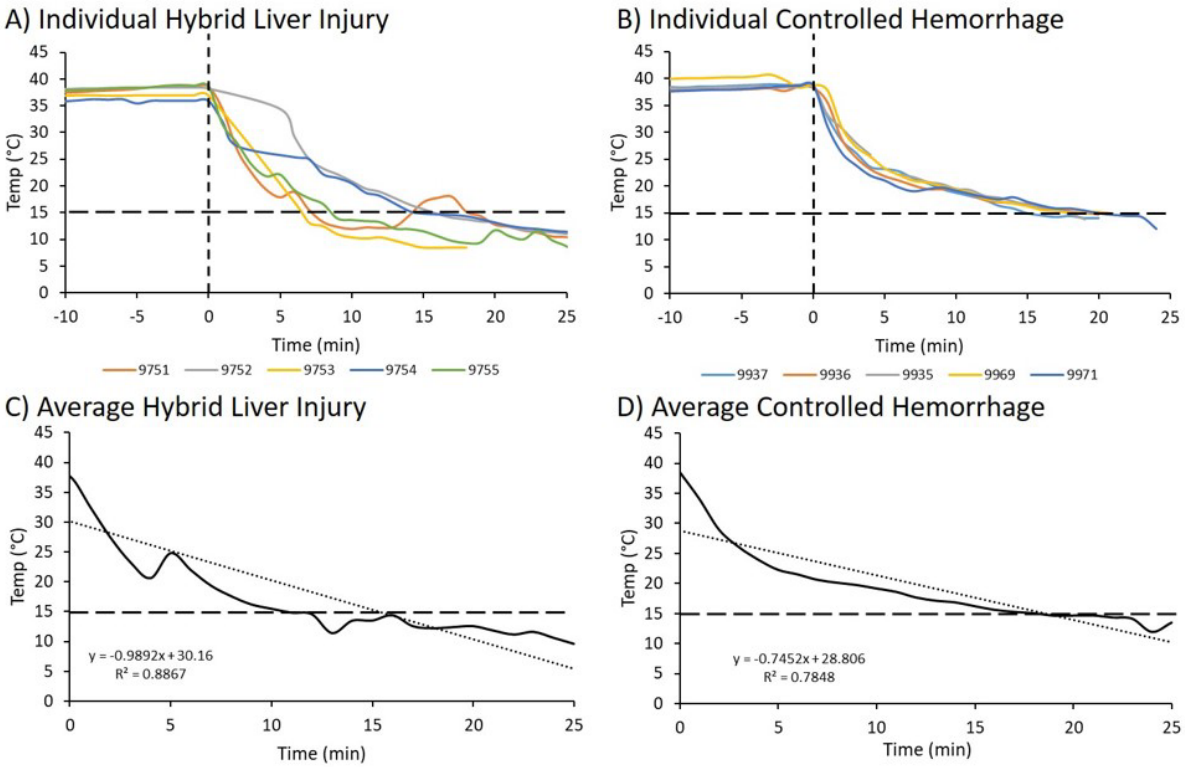

Figure 5. Pulmonary Artery Temperatures
A) Individual subject temperatures are shown for hybrid liver injury. **B)** Individual subjects for controlled hemorrhage. **C)** Average temperature for all Hybrid liver injury subjects is shown with trendline and corresponding equation. **D)** Average temperature for all controlled hemorrhage subjects. Vertical dashed line represents initiation of hypothermia in A and B. Horizontal dashed line represents target temperature.

Brain temperatures during hypothermia induction are shown in Figure 6. Overall, brain temperatures of both groups were 37.9 ± 0.9 at baseline with no significant difference between groups. Individuals are shown in the top panels for both groups, while mean temperatures are shown in the bottom panels C and D. The rate of cooling for each group is shown as the slope of the trendline. The hybrid liver injury group averaged a decrease in brain temperature of 0.3°C/min, while the controlled hemorrhage group was 0.5°C/min. Three subjects in the hybrid liver injury group and two subjects in the controlled hemorrhage group did not achieve any appreciable cooling. Only one subject (9936) out of both groups reached the target brain temperature of 15°C with a rate of 2.1°C/min.

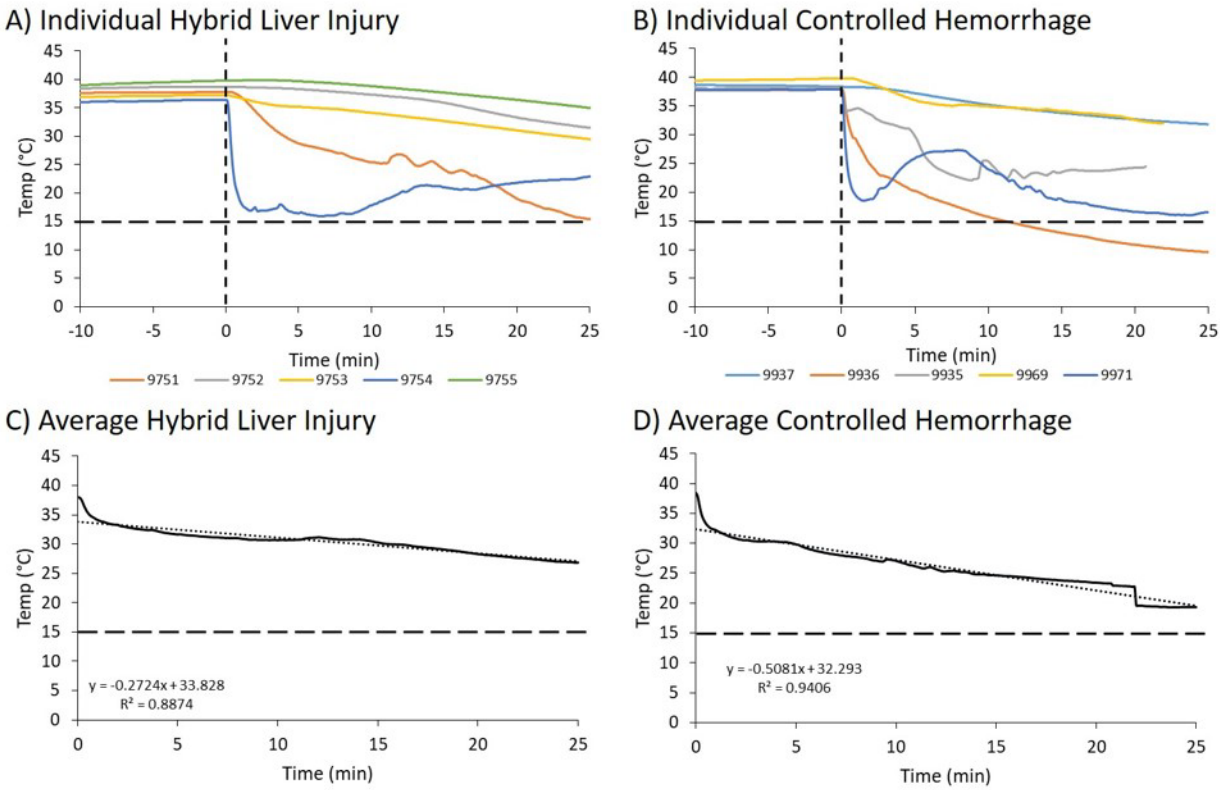

Figure 6. Brain Temperatures

A) Individual subject temperatures are shown for hybrid liver injury. **B)** Individual subjects for controlled hemorrhage. **C)** Average temperature for all Hybrid liver injury subjects is shown with trendline and corresponding equation. **D)** Average temperature for all controlled hemorrhage subjects. Vertical dashed line represents initiation of hypothermia in A and B. Horizonal dashed lines represent goal temperature.

7.3 Hemodynamics

A summary of the hemodynamics characteristics of the two groups is shown in Figure 7. MAP was exceedingly low during the arrest period just before the vertical dashed line representing the start of hypothermia induction through the SAAP catheter. Both groups showed a large increase in MAP and blood flow immediately following SAAP infusion. Conversely, MPAP and CVP increase following SAAP infusion was slower in both groups. MAP and flow were observed to be lower than normal physiologic values, while MPAP and CVP were both higher than normal indicating some pulmonary congestion. Interestingly, these values approached or exceeded the pressure in the carotid proximate to the SAAP catheter.

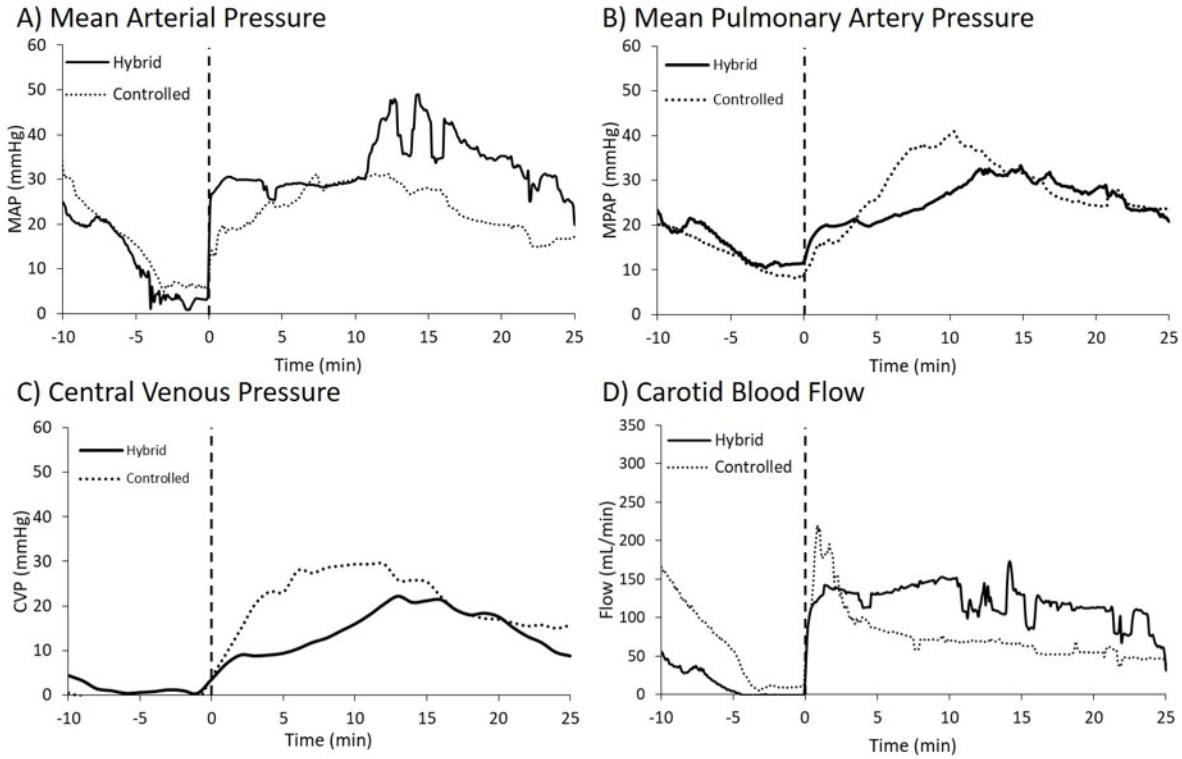

Figure 7. Hemodynamics
A) Mean Arterial Pressure (MAP) recorded from carotid artery. **B)** Mean pulmonary artery pressure (MPAP) recorded from Swan-Ganz catheter. **C)** Central venous pressure (CVP) recorded from Swan-Ganz. **D)** Flow recorded using a flow probe on carotid artery. All values are average of all subjects. Dashed line represents initiation of hypothermia.

7.4 Rewarming

Rewarming was attempted on two subjects from the controlled hemorrhage group (Figure 8). Subject 9936 and 9971 reached 9.6°C and 16.0°C respectively before rewarming commenced. The average warming rate was 0.65°C/min for brain temperature rewarming and 0.67°C/min for pulmonary artery temperature rewarming as measured by the Swan-Ganz catheter. A steady increase in temperatures was observed in all measurements except for subject 9936 who did not have any appreciable warming noted in the pulmonary artery. 9971 reached 33.4°C and had all blood products returned. Countershocks were not performed as a regular, but abnormal cardiac rhythm was observed on ECG. Unfortunately, this rhythm was not sufficient enough to bring MAP above 20mmHg which met death criteria.

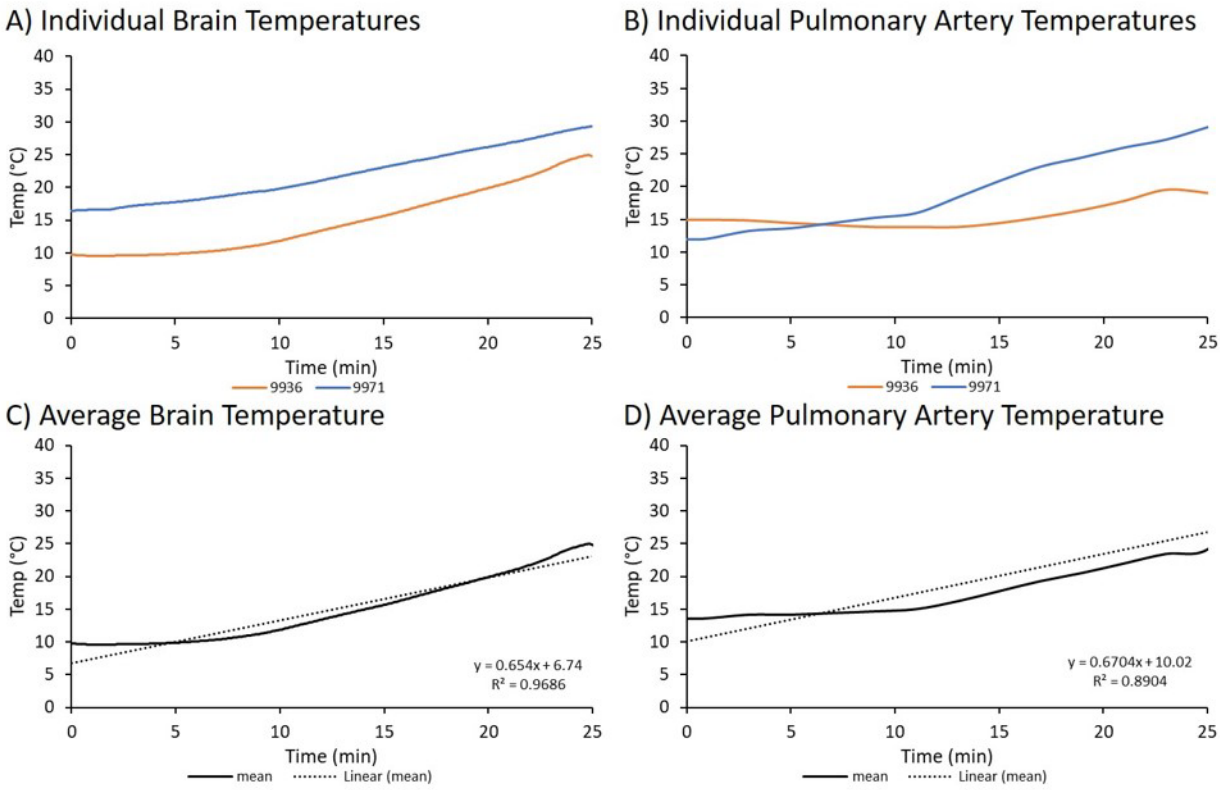

Figure 8. Rewarming
A) Individual brain temperatures during rewarming. **B)** Individual pulmonary artery temperatures. **C)** Average brain temperature of subjects in A). **D)** Average brain temperature of subjects in B). All values are average of all subjects. Dashed line represents initiation of hypothermia. Dotted lines are trendlines of average temperatures. Equation for trendline and R^2 are also shown.

8.0 DISCUSSION

Hemorrhage is associated with most of the potentially survivable deaths on the battlefield. The end result of this type of hemorrhage is HiTCA. There are currently few treatments that are effective in treating HiTCA. EPR is a method of extending the window to treat injuries that lead to cardiac arrest and/or extend the time of organ viability following hemorrhage. EPR has been shown to be successful in the laboratory environment extending tissue preservation for up to 90 minutes with positive neurologic outcome.

This project was undertaken to determine the feasibility and practicality of utilizing the novel SAAP catheter to induce EPR in a swine model of HiTCA. SAAP is a method that uses a REBOA-like catheter with a large central lumen designed to deliver fluids rapidly to the aortic arch. SAAP was designed to treat TCA but also serves as a hemorrhage control adjunct similar to REBOA. In situations of definitive care, SAAP could be used to treat TCA, but in situations where EPR is necessary, SAAP would instead be helpful to induce profound hypothermia and EPR. Therefore, the SAAP catheter could provide multifunctional support for victims of HiTCA.

The main outcome of the study was to determine if the SAAP catheter could be used to induce profound hypothermia (<15°C) in the brain of subjects following HiTCA. Intracranial temperatures were the main outcome due to the brain being the most important and most sensitive tissue to ischemia. Only one subject out of all those entered into the study had the required rate of 2°C/min. Two subjects, one from each group, had initial rapid drops in temperature reaching below 20°C in less than two minutes, but neither attained the goal temperature of 15°C. This low level of success shows that the technique has an inadequate efficacy in its current form. However, it is possible that further optimization of the technique could improve the rate of cooling.

One possibility of why the rates of cooling were not as quick as anticipated could be the flow rate of the cold fluid reaching the brain. Flow measurements from the carotid artery were substantially lower than the flow rates in the carotid artery prior to injury. Normal flow rates in our lab were recorded in the 300-500 mL/min range, while the flow rates during hypothermia induction were 100-200 mL/min. Other methods of inducing hypothermia are typically at 3-4 L/min, while those in this study reached up to 750mL/min which suggested this as the possible reason for the lack of success when using the SAAP for EPR. Interestingly enough, subject 9936 had flow rates that never exceeded 100 mL/min noting that a high flow rate may not be necessary for reaching the desired rate of cooling.

Half of the subjects enrolled in the study did not have any appreciable cooling and never reached a temperature lower than room temperature (25°C). No obvious correlation exists between any factors examined in these groups in their inability to achieve profound hypothermia. MAP, MPAP, CVP, and flow were not indicative of failure. Localized backpressure in the brain, formation of thrombi despite use of heparin or vasoconstriction are likely causes.

Two animals were rewarmed according to protocol. The average rewarming for both brain and pulmonary artery was greater than the desired temperature increase of 0.5°C/min indicating that the SAAP catheter and associated circuit are capable of successfully supporting the rewarming procedure. The rate of warming could easily be slowed down by adjusting the heater or changing the flow rates. One of the subjects was halted due to substantial clotting in the circuit, but the other subject had an organized cardiac rhythm. This rhythm was not productive, but with acid/base balance balancing and vasopressor support, this subject may have achieved better outcomes.

Future studies involving SAAP and the induction of profound hypothermia for EPR should address the lack of efficacy to rapidly cool the brain. Testing and evaluation of a modified SAAP catheter that has a larger

central lumen capable of faster infusion may provide valuable information on the feasibility of real world use. The utilization of larger, multi-hole venous catheters would likely provide an increase in efficacy. However, the recent work by Liu et al. has shown that venous-arterial ECMO can be successfully used to induce profound hypothermia. ECMO is becoming more clinically-relevant, and the use of EPR could be integrated into facilities with ECMO capabilities and expertise.

9.0 DELIVERABLES

9.1 Publications

9.2 Presentations

- Poster presentation at the 2019 San Antonio Military Health System and University Research Forum (SURF)

10.0 COST

This work was selected and funded by the Air Force Medical Support Agency (AFMSA) funding under project code number AC16EC02. This project received AC6 funds on 23 June 2016 ($250K), AC7 funds on 8 Aug 2017 ($252K), and AC8 funds on 5 Apr 2018 ($254K).

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12.0 LIST OF SYMBOLS, ABBREVIATIONS, AND ACRONYMS

CVP	Central Venous Pressure
ECMO	Extracorporeal Membrane Oxygenation
EPR	Emergency Preservation and Resuscitation
$ETCO_2$	End-Tidal Carbon Dioxide
FiO_2	Fraction of inspired oxygen
H_2S	Hydrogen sulfide
HiTCA	hemorrhage-induced traumatic cardiac arrest
MAP	Mean Arterial Pressure
MPAP	Mean Pulmonary Artery Pressure
NCTH	Non-Compressible Torso Hemorrhage
REBOA	Resuscitative Endovascular Occlusion of the Aorta
ROSC	Return of Spontaneous Circulation
SAAP	Selective Aortic Arch Perfusion
SBP	Systolic Blood Pressure
SVO_2	Mixed Venous Oxygen Saturation
TTM	Targeted Temperature Management