## Development of the emergency preservation and resuscitation for cardiac arrest from trauma clinical trial

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BACKGROUND: Patients who suffer a cardiac arrest from trauma rarely survive, even with aggressive resuscitation attempts, including an emer-

> gency department thoracotomy. Emergency Preservation and Resuscitation (EPR) was developed to utilize hypothermia to buy time to obtain hemostasis before irreversible organ damage occurs. Large animal studies have demonstrated that cooling to tympanic membrane temperature 10°C during exsanguination cardiac arrest can allow up to 2 hours of circulatory arrest and repair of

simulated injuries with normal neurologic recovery.

The Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma trial has been developed to test the feasibility and STUDY DESIGN:

> safety of initiating EPR. Select surgeons will be trained in the EPR technique. If a trained surgeon is available, the subject will undergo EPR. If not, the subject will be followed as a control subject. For this feasibility study, 10 EPR and 10 control subjects

STUDY PARTICIPANTS:

Study participants will be those with penetrating trauma who remain pulseless despite an emergency department thoracotomy. INTERVENTIONS: Emergency Preservation and Resuscitation will be initiated via an intra-aortic flush of a large volume of ice-cold saline solution.

Following surgical hemostasis, delayed resuscitation will be accomplished with cardiopulmonary bypass.

**OUTCOME MEASURES:** The primary outcome will be survival to hospital discharge without significant neurologic deficits. Secondary outcomes include

long-term survival and functional outcome.

**IMPLICATIONS:** Once data from these 20 subjects are reviewed, revisions to the inclusion criteria and/or the EPR technique may then be tested in a

second set of EPR and control subjects. (J Trauma Acute Care Surg. 2017;83: 803-809. Copyright © 2017 Wolters Kluwer

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**KEY WORDS:** Cardiac arrest; cardiopulmonary bypass; hemorrhagic shock; hypothermia; trauma.

**E** xsanguinating hemorrhage, leading to cardiac arrest or multiple organ failure, is the most common cause of death in trauma patients without traumatic brain injury. Standard resuscitation of trauma victims who develop cardiac arrest from exsanguination includes airway management, volume resuscitation, and, in selected patients, emergency department (ED) thoracotomy with open-chest cardiopulmonary resuscitation (CPR). The chest is opened with the hope of finding an intrathoracic injury that can be quickly repaired and to occlude the descending thoracic aorta to maximize blood flow to the most vulnerable organs, brain and heart. Unfortunately, the brain and heart can only tolerate complete ischemia of approximately 5 and 20 minutes, respectively, at normothermia before suffering significant damage. Consequently, the overall survival is only 7% at best, although more than 90% of survivors have normal neurologic outcomes. Several factors seem to influence survival rates: (1) mechanism of injury (penetrating better than blunt), (2) location of

injury (thoracic better than abdominal or multiple), and (3) signs of life in the field or on arrival at the hospital. Electrocardiographic findings of asystole or pulseless electrical activity with bradycardia are associated with a low likelihood of survival. Recognizing the frequent futility of resuscitative efforts in patients who have suffered cardiac arrest from trauma, guidelines have been developed for withholding or terminating resuscitation.<sup>2</sup> Clearly, current resuscitation strategies are inadequate; novel approaches are needed.

In 1984, Col. Ronald Bellamy<sup>3</sup> and Dr. Peter Safar reviewed military casualty data from the Vietnam War. Approximately 80% of soldiers killed in action in Vietnam without brain trauma had penetrating truncal injuries. They rapidly exsanguinated internally. Many had technically repairable injuries upon autopsy. Bellamy et al.<sup>4</sup> proposed a novel approach, Emergency Preservation and Resuscitation (EPR), to managing such patients utilizing hypothermia, drugs, and specialized fluids to produce a state of ischemic tolerance to provide the surgeon with sufficient time during pulselessness to control hemorrhage, to be followed by delayed resuscitation.

## LABORATORY STUDIES

Researchers at the Safar Center for Resuscitation Research (SCRR) of the University of Pittsburgh began systematic outcome studies in dogs for the development of EPR in 1989. In the initial series of experiments, following 30 minutes to 60 minutes of severe hemorrhagic shock, hypothermia was induced by closed-chest cardiopulmonary bypass (CPB).5,6

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Circulatory arrest periods of 60 minutes to 120 minutes were explored, with CPB for reperfusion and rewarming. All animals survived; the main outcome variable was neurologic function. Profound cerebral hypothermia (tympanic membrane temperature [Tty] 10°C) induced at the beginning of exsanguination cardiac arrest of 2 hours improved neurologic outcome compared with that with deep hypothermia (15°C).<sup>7</sup>

Clinically, full CPB cannot be initiated within the critical 5 minutes of cardiac arrest. Rapid placement of an aortic catheter could allow targeting of the brain and heart with a flush of cold fluid. Subsequent studies at the SCRR have utilized a catheter placed via the femoral artery for flushing the aorta directly with 0°C to 4°C, 0.9% saline at a rate of 1 L/min to 2 L/min, lowering Tty by approximately 3°C/min. The model included rapid, controlled hemorrhage via catheters in the aorta and vena cava over 5 minutes to cardiac arrest (which was ensured by inducing ventricular fibrillation). The cold flush was started at 2 minutes of arrest, with drainage via the vena cava catheter. The period of circulatory arrest was varied from 15 minutes to 180 minutes, with preservative Tty levels decreasing from 34°C to 10°C. 8-11 Reperfusion and rewarming were accomplished with closedchest CPB. Postresuscitation mild hypothermia (34°C), which seemed beneficial in patients after nontraumatic cardiac arrest, 12,13 was continued to 12 hours, and intensive care to 72 hours to 96 hours.

Lower intra-arrest temperatures were required to achieve normal recovery after longer arrest times. Beyond 20 minutes, it seemed that spinal cord ischemia was a problem, manifest as hind-leg weakness. <sup>8,10,11</sup> For longer periods of arrest, total body cooling was accomplished via a large-bore cannula placed in the femoral artery. Cooling to Tty 10°C with very large amounts of flush (500 mL/kg over 15 minutes) was required to achieve intact survival after 60-minute to 120-minute EPR. <sup>9</sup>

Pharmacologic approaches with novel drugs and solutions would be advantageous for induction of EPR by synergizing with hypothermia and perhaps decreasing the volume of flush required. Fourteen different drugs for cerebral preservation were tested. <sup>14–17</sup> Only the antioxidant tempol gave a suggestion of benefit. <sup>16</sup> Both the SCRR and Massachusetts General Hospital groups have conducted studies to better understand the biological mechanisms underpinning ischemia and reperfusion injury in this model in order to optimize its protective efficacy. <sup>18–25</sup> Results of these studies may provide the basis for future outcome studies of EPR.

Providing energy substrate could be beneficial during EPR. A study of an energy preservation strategy using oxygen and glucose added to the flush solution allowed some intact survivors after 3 hours of circulatory arrest at Tty 10°C.<sup>26</sup>

In the studies described previously, readily available fluids were utilized. Special solutions, such as "Unisol" (two solutions: an "intracellular fluid" and an "extracellular fluid") designed by Taylor et al.<sup>27</sup> (Organ Recovery Systems Co.) might have some benefit. Unisol-I (intracellular type) was intended for preserving kidneys for transplantation and has 70 mEq/L of potassium, which immediately arrests metabolism by making the sodium-potassium channel unavailable. For resuscitation, the CPB reservoir fluid was exchanged with Unisol-E-K—free (extracellular, potassium-free) to reverse the hyperkalemia. The Unisol solutions have been used successfully by the groups at Uniformed Services

University of the Health Sciences and Massachusetts General Hospital (led by Drs. Rhee et al.<sup>29</sup> and Alam et al.<sup>28</sup>). Controlled studies comparing different fluids are needed.

Rhee et al. <sup>29</sup> and Alam et al. <sup>28</sup> have explored EPR in a clinically relevant exsanguination model in pigs. Because an ED thoracotomy is standard for exsanguinated patients, they created a model of traumatic exsanguination via a thoracotomy and aortotomy. They directly cannulated the aorta and induced profound hypothermia by aortic flush using Unisol. Repair of the aortotomy was accomplished during no, or trickle, flow, which made the repairs simpler. Normal cognitive function after exsanguinating hemorrhage and prolonged asanguineous low flow (by CPB) at 10°C could be achieved. <sup>28,30</sup> They found a suggestion that best outcome is with the most rapid cooling and moderately slow rewarming. <sup>31,32</sup>

Exsanguinating hemorrhage in trauma patients does not occur without significant tissue trauma. Adding tissue trauma to the SCRR 60-minute EPR model in the form of thoracotomy, laparotomy, and splenic transection (splenectomy performed during arrest) led to survival, but with coagulopathy and multiple organ dysfunction, which was not seen without trauma. Using low-flow CPB with profound hypothermia, Sailhamer et al. 4 have also demonstrated that clinically relevant injuries can be repaired and normal outcome achieved with EPR.

Wu et al.<sup>35</sup> compared 1 hour of EPR with standard care (closed-chest CPR and fluid resuscitation) following cardiac arrest from prolonged hemorrhage (~2 hours) and trauma induced via a laparotomy and splenic transection. There were no long-term survivors in the standard care group; all developed irreversible multiple organ failure. Even with 1 hour of hypothermic noflow following prolonged hemorrhagic shock, however, almost all dogs survived in the EPR groups. Prolonging the period of postresuscitation mild hypothermia to 36 hours, rather than 12 hours, seemed to further improve neurologic outcome.

In summary, outcomes from cardiac arrest in trauma patients with current management strategies are dismal. Laboratory studies suggest that EPR holds promise for improving these outcomes. Sufficient data are available from studies carried out in clinically relevant, large animal models to justify and develop a clinical feasibility study.

## CLINICAL EPR PROTOCOL DEVELOPMENT PROCESS

The development of the EPR protocol began with a meeting of experts in the fields of trauma, critical care, emergency medicine, and military medicine, as well as members of the University of Pittsburgh Institutional Review Board (IRB). The initial protocol included the following points:

- Patient inclusion/exclusion criteria are listed in Table 1.
- Emergency Preservation and Resuscitation would be achieved by inserting a CPB cannula into the descending aorta via an aortotomy with venous drainage by placing a CPB cannula into the right atrium.
- Cold saline would be infused retrograde into the aorta using a CPB pump. If possible, blood could be recirculated from the venous cannula or pump suction in the chest.
- A heparin-bonded CPB circuit would be used.

#### TABLE 1. Enrollment Criteria

#### Initial Criteria

#### Revised Criteria\*

#### **Inclusion Criteria**

Blunt or penetrating trauma with clinical suspicion of exsanguinating hemorrhage

Aged 18-65 y

At least one sign of life at the scene (pulse, respiratory efforts, spontaneous movements, reactive pupils)

Loss of pulse <5 min prior to ED arrival or in the ED

Thoracotomy performed in the ED without immediate return of a palpable pulse

#### **Exclusion Criteria**

Obvious nonsurvivable injury Evidence of traumatic brain injury Electrical asystole

Massive tissue trauma involving multiple body regions

Pregnancy

Penetrating trauma with clinical suspicion of exsanguinating hemorrhage

Aged 18-65 y

At least one sign of life at the scene (pulse, respiratory efforts, spontaneous movements, reactive pupils)

Loss of pulse <5 min prior to ED arrival or in the ED or OR

Thoracotomy performed in the ED *or OR* without immediate return of a palpable pulse

Obvious nonsurvivable injury Evidence of traumatic brain injury Electrical asystole

Massive tissue trauma involving multiple body regions

Pregnancy Prisoners

Military personnel

An aortic arch injury that would preclude flush

- Once the subject is cooled to the goal temperature (Tty 10°C), the subject would be transported to the operating room (OR) for a damage control procedure.
- Once hemostasis is achieved, reperfusion and slow rewarming can begin via the CPB system.
- The goal should be to rewarm to 34°C. Mild hypothermia at this
  level would be continued to 12 hours unless the subject has severe
  coagulopathy, necessitating further rewarming for hemostasis.
- Training should include trauma and cardiac surgeons, as well as perfusionists.
- Subjects should not be enrolled unless the trained team members are available. Subjects who meet the entry criteria, but do not have EPR initiated because the trained team is not available, would serve as control subjects.

The sample size should be 50 subjects in each of the EPR and control groups. This was based on expected survival of less than 10% for this group of patients with standard resuscitation attempts. As this is a Phase II trial to establish the potential for improved outcome in this patient population, this number of subjects could demonstrate benefit with as few as seven to eight survivors of 50 subjects.

## FOOD AND DRUG ADMINISTRATION

Application for an Investigational Device Exemption was submitted to the Food and Drug Administration (FDA) based on the trial design outlined above, as the use of saline and CPB equipment in this manner is considered investigational. The FDA suggested starting with enrolling and obtaining outcome data on 10 subjects who undergo EPR and 10 control subjects.

Based on the outcomes, the investigators could propose changes to the selection criteria or the EPR technique. With a revised protocol, another 10 EPR and 10 control subjects could be enrolled. This iterative process could continue until the investigators and the FDA believe that the optimal protocol has been developed for a definitive trial. The FDA proposed including historical data on potential EPR subjects to avoid the risk of bias if the EPR team is less available at night, and nighttime trauma care differs from daytime care.

The FDA expressed concern about the heparin bonding for the CPB system because of reports of contaminated heparin. They asked the investigators to provide detailed information about the cannula manufacturing process.

The FDA suggested that the best primary end point for this study would be survival to hospital discharge without severe disability (Glasgow Outcome Scale—Extended [GOSE] score >5). Given the risk involved in this study, the FDA has asked for an interim report after five EPR and five control subjects have been enrolled. After 10 subjects have been enrolled in each group, enrollment in the study will be suspended while a final report is completed and reviewed.

Once the FDA approved the study, the study was posted on clinicaltrials.gov (NCT01042015).

## **CONFLICT OF INTEREST**

Because the principal investigator (PI) (S.A.T.) and a coinvestigator (P.M.K.) have a conflict of interest as coauthors of a patent (US 8,628,512 B2) for "Emergency Preservation and Resuscitation Methods," the study was referred to the University of Pittsburgh research integrity officer and Conflict of Interest Committee and the University of Maryland Baltimore conflict of interest officer. The conflict of interest management plan consisted of (1) establishment of an independent data stewardship committee, (2) stipulation that the PI will not be involved in recruitment of subjects, recording of research data, or determination of subjects' outcomes. The PI can still report to the independent Data Safety Monitoring Board (DSMB), but cannot be involved in their decision making. He can be involved in the interpretation of study results, but cannot be the sole evaluator. In addition, specific language regarding the conflict of interest must be included in consent forms, community consultation and public disclosure information, and publications of the research. All coinvestigators and research staff were notified of the conflict of interest. A nonconflicted coinvestigator agreed to answer any questions from subjects, legally authorized representatives (LARs), or the public regarding the conflict of interest.

### **INSTITUTIONAL REVIEW BOARDS**

The major hurdle for the IRB process at the University of Pittsburgh and the University of Maryland was managing the exception from informed consent because subjects to be enrolled in this study will not be able to give prospective, informed consent. This study meets all the criteria for an exception from informed consent for emergency research under 21 CFR 50.24. Consent would be obtained from the subject or subject's LAR for continued participation. In addition, letters

<sup>\*</sup>Changes from the initial criteria are in italics

would be sent to the relatives of subjects who die before they can be contacted directly.

Because the funding for the study comes from the Department of Defense, the US Army Medical Research and Materiel Command (USAMRMC) Research Ethics Advisory Panel needed to conduct a review of the protocol and consider a request for a 10 USC 980 waiver of prospective informed consent, which had to be approved by the Secretary of the Army. The community consultation plan could not be initiated until this waiver had been approved.

# COMMUNITY CONSULTATION AND PUBLIC DISCLOSURE

Community consultation included presentations to town hall-type events at the University of Pittsburgh and meetings with the Pittsburgh Commission on Human Relations and the University of Pittsburgh Center for Minority Health Community Research Advisory Board. Attendees were invited to fill out a survey. These groups recognized the potential benefit of the study to subjects, but raised concerns about conducting this study in a penetrating trauma population, particularly young African American males, whom may be difficult to reach during the community consultation and public disclosure process. Because of the concerns raised, the community consultation process was revised to include a random-digit dialing survey using the UPMC Presbyterian Trauma Registry to focus on the communities at greatest risk of becoming trauma victims. This survey revealed that the majority of respondents (~70%) would be willing to participate themselves or to have a family member participate in the study, although there was some variability based on age, gender, education level, and income. A similar survey was placed in trauma clinic with similarly favorable interest in the study.

Public disclosure was initiated with a press release. There was significant national interest after the Associated Press covered the story. The study has been advertised on acutecareresearch.org, which advertises throughout Pittsburgh. This Web site allowed members of the public to submit comments to the researchers.

Members of the community have the opportunity to request an opt-out wristband via the Web site. This information was included in the community meetings, as well as in the press release, discussions with members of the press, and the Web site.

The process in Baltimore began with a press release that was picked up by local media. The PI and study coordinator attended several public events. A Web site was developed (www.eprstudy. com) that provided more information for the public, as well as allowed comment and request for an opt-out wristband. Surveys were distributed at the public events and in trauma clinic; they were also available on the Web site. Respondents to the survey were highly supportive (>90%) of the study.

## **DATA SAFETY AND MONITORING**

The independent DSMB consists of a trauma surgeon, cardiothoracic surgeon, a military surgeon, and an emergency physician. The FDA agreed with our recommendation that the DSMB review each case via teleconference. In addition to the DSMB, the US Army mandates that each site have a medical

monitor, an individual not involved in the research who is in an appropriate clinical position to be able to intervene if the subject suffers a complication of the research-related procedures.

The DSMB has met annually via conference call. They have recommended the following: (1) blunt injury should be an exclusion criterion given the dismal outcomes with current levels of care; (2) aortic cannulation should be accomplished using the Seldinger technique; and (3) follow-up should include quality-of-life data and should be extended to 12 months. They further recommended that the trauma surgeons trained to initiate EPR obtain approval from the hospital credentials committee.

#### **TRAINING**

Training the team to initiate EPR is critical to the success of the trial. Consequently, the protocol includes a multifaceted approach to training, including the use of animals, cadavers, and full-scale human simulation.

To include these training sessions in the protocol, approval was obtained from the Universities of Pittsburgh and Maryland Institutional Animal Care and Use Committees, as well as the Office of Research Protections Animal Care and Use Review Office of the USAMRMC. Two swine experiments were conducted at each site for the EPR-trained trauma surgeons, cardiac surgeons, and perfusionists.

For the use of cadavers for training, the study was approved by the University of Pittsburgh Committee for Oversight of Research and Clinical Training Involving Decedents, the Maryland State Anatomy Board, and the USAMRMC Office of Research Protections. The cadaver dissections demonstrated that transection of the sternum (i.e., clamshell thoracotomy) will be required to obtain adequate access to the right atrium.

As a means to practice the steps involved in the initiation of EPR without live animals or cadavers, the teams have also run through the process in the simulation laboratory. Such "dry runs" allow the surgical team and other personnel to practice EPR initiation as frequently as needed to be well prepared for this rare procedure. During these training sessions, the subject inclusion criteria and the potential risks (including the need for extracorporeal life support, coagulopathy, multiple organ failure, survival with neurologic deficits, and death) are reviewed.

## LESSONS LEARNED FROM TRAINING

Attempts at recirculating fluid through the CPB circuit during the cooling process lead to clotting of the bypass circuit, even when the blood was massively hemodiluted, raising concerns about withholding systemic heparin during reperfusion, even with heparin-bonded CPB equipment. With these issues in mind, decisions were made to (1) cool with an arterial flush alone, discarding all the venous effluent, and (2) use heparin during full CPB resuscitation, negating the need for heparin-bonded equipment. The DSMB, FDA, and IRBs agreed with these changes in the protocol.

During the preparation for subject enrollment in the trial, the trauma service at the University of Pittsburgh noted that there had been some patients who physiologically might have benefited from EPR, but did not suffer cardiac arrest until they were in the OR. The study protocol was revised to include potential enrollment in the OR and approved by the DSMB, FDA, and IRBs accordingly.

#### **FINAL PROTOCOL**

The final subject enrollment criteria are listed in Table 1. The study protocol is outlined in Figure 1. Ten subjects who undergo EPR and 10 subjects who meet the enrollment criteria, but are not enrolled because a trained trauma surgeon is not available, will be enrolled, and a detailed report will be submitted to the FDA prior to any further subject enrollment.

Subjects entered into this trial will have had a left thoracotomy with clamping of the distal thoracic aorta unless resuscitative endovascular balloon occlusion of the aorta (REBOA) has already been placed. Appropriate operative exposure for EPR will require transection of the sternum and extension of the thoracotomy to the right (i.e., clamshell thoracotomy). The trauma surgeon will place an arterial cannula (17–21 Fr) for the EPR flush into the aorta using a Seldinger technique. The cannula will be connected to the pump and secured with a purse string suture. The immediate goal is to maximize flow to the brain and heart. The flush will be with ice-cold 0.9% saline via a CPB roller pump at a minimum of 2 L/min. Flow will be

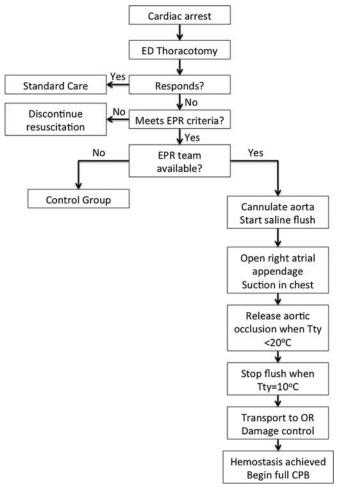


Figure 1. Emergency Preservation and Resuscitation algorithm.

increased as tolerated, with an expected maximum of 5 L/min. Once the flush begins, the right atrial appendage will be opened. Venous effluent that drains into the chest will be discarded. During cooling, tympanic or nasopharyngeal (Tnp) temperature will be monitored as a noninvasive estimate of brain temperature. A rectal temperature probe or Foley catheter with temperature sensor will also be inserted to monitor total body cooling for EPR. Once the Tty or Tnp has reached 20°C, the aortic clamp will be released slowly, monitoring CPB flow, to allow whole-body cooling. Cooling will continue until Tty or Tnp is 10°C, and rectal temperature is less than 30°C.

When the subject reaches the goal temperature, the pump will be stopped until hemostasis has been secured. The subject will be transported immediately to the OR for resuscitative surgery. The operative approach will be focused on damage control. All surgical fields will remain open for observation during reperfusion and rewarming to ensure hemostasis. During the operation, the cardiac surgeon will place a venous cannula for full CPB. The aortic cannulation may be transferred to the arch at the cardiac surgeon's discretion. This will allow repair of the aortotomy performed in the ED.

The surgeon may elect to discontinue resuscitative efforts if technical issues, for example, cannulation difficulties or pump dysfunction, preclude cooling, or if nonsurvivable injuries are identified.

Once hemostasis has been achieved, CPB will be initiated for reperfusion and slow rewarming. The goal will be to keep the total time of circulatory arrest under 1 hour and to minimize the duration of low flow at profound hypothermia. The rewarming rate will be targeted at 0.5°C/min. During rewarming, blood products will be transfused. Intravenous heparin will be administered as needed until CPB is discontinued.

Rewarming will continue until Tty reaches 36°C, which will be maintained for 24 hours to optimize neurologic recovery. Shivering will be treated with sedation and, if necessary, neuromuscular blockade. Temperature control to prevent fever will be continued until 72 hours.

Decannulation should be performed as soon as the subject has sufficiently stable spontaneous circulation to be weaned from CPB. If the subject requires more prolonged circulatory support, the use of extracorporeal life support via extrathoracic (usually femoral or jugular) cannulation can be considered. Extracorporeal life support may be appropriate for a subject who cannot be weaned from CPB because of hypotension (despite inotropes/vasopressors) or inadequate oxygenation (e.g., Pao<sub>2</sub>-to-Fio<sub>2</sub> ratio consistently <100), yet otherwise seems to have potential for long-term survival.

### **Historical Control Group**

Because of concern that bias related to trained team availability may influence the selection of subjects who receive EPR, outcome information regarding similar patients in the trauma registry of the respective institutions will be obtained.

## Consent

Once the subject has been stabilized, consent for continued participation in the study for collection of data and long-term follow-up will be obtained from the subject's LAR or the subject. Similarly, consent for follow-up will be obtained for survivors in the control group. For subjects who die before the research

coordinator or an investigator has been able to discuss the study with the LAR, a letter will be sent to the LAR explaining the study and offering contact information for further information.

### **Outcome**

The primary outcome variable will be survival to hospital discharge without major disability (Glasgow Outcome Scale—Extended [GOSE] score >5). Secondary outcomes will include (1) the feasibility and safety of rapidly inducing profound cerebral hypothermia for EPR in exsanguinating trauma patients, (2) 28-day survival, (3) 6- and 12-month neurologic functional outcome (Glasgow Outcome Scale—Extended [GOSE] score) and SF-36, and (4) the development of multiple organ dysfunction syndrome in the EPR group, as compared with a concurrent control group and historical control subjects. Specific complications related to the implementation of EPR and CPB, such as vascular injuries, will be identified.

### **FUTURE STUDIES**

The decision to proceed with further clinical investigation of the EPR technique will depend on the frequency of associated complications and lack of inferiority to standard care with regard to the secondary end points. Based on the experience from this study, the entry criteria may be revised in order to select subjects most likely to benefit from the intervention. The technique for EPR may also be revised. Evaluating these new criteria or techniques may justify further investigation.

If laboratory research studies demonstrate significant benefits from pharmacologic approaches or specially designed fluids, these could be tested. New devices that would help facilitate implementation of EPR also warrant testing.

The approach to the management of the trauma patient who has suffered a cardiac arrest may be changing. Some centers are using REBOA and closed-chest CPR, rather than an ED thoracotomy, for selected patients who suffer a cardiac arrest from trauma. If such patients do not respond, they could represent good candidates for EPR. Cannulation for EPR would then require a thoracotomy. An algorithm for managing the exsanguinating patient using REBOA and/or EPR could be developed and tested.

#### **AUTHORSHIP**

All authors have contributed to the design of this study. S.A.T. drafted the manuscript. All authors were actively involved in the critical revision of the manuscript.

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#### **DISCLOSURE**

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