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Review

Emergency preservation and resuscitation for cardiac arrest from trauma

Matthew E. Kutcher [a, *], Raquel M. Forsythe [a], Samuel A. Tisherman [b]

[a] Division of Trauma and General Surgery, Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
[b] Department of Surgery, RA Cowley Shock Trauma Center, University of Maryland School of Medicine, Baltimore, MD, USA

HIGHLIGHTS

- Standard CPR is ineffective in traumatic cardiac arrest.
- Profound hypothermia extends the time window for repair of exsanguinating injuries.
- A clinical trial of hypothermia induction for traumatic arrest is now enrolling.
- Emergency preservation and resuscitation (EPR) is an active area of trauma research.

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ABSTRACT

The advent of cardiopulmonary resuscitation (CPR) revolutionized the care of patients with cardiac arrest, now allowing survival of up to 30% after out-of-hospital arrest due to arrhythmia; however, outcomes for cardiac arrest after trauma remain dismal, with less than 10% survival despite the most aggressive modern resuscitation techniques. The short time interval between cardiac arrest and brain ischemia, the reduced efficacy of CPR in the patient with profound hypovolemia due to hemorrhage, and the speed of exsanguination from major vascular injury all conspire to limit the effectiveness of standard CPR in the critically injured patient.

Beginning in the 1980s, researchers began to harness the effects of profound hypothermia in order to extend the window of survivability after traumatic arrest, allowing the critical time needed to obtain surgical hemostasis in otherwise lethal exsanguinating injuries. These studies have culminated in the emergency preservation and resuscitation (EPR) of the trauma patient. Rapid central arterial access is obtained and profound (<10 °C) hypothermia induced with aortic infusion of cold saline. During this window of up to 1 h, damage control surgical techniques are applied to control hemorrhage and repair injuries, followed by controlled rewarming and reperfusion using cardiopulmonary bypass. In this review, we trace these techniques from their early theoretical development, through refinement in clinically relevant animal models, and into their present application in a currently-enrolling human clinical trial of EPR for cardiac arrest from trauma (EPR-CAT), as well as examine current topics, ongoing challenges, and future directions for emergency preservation and resuscitation research.

1. Introduction

Cardiopulmonary resuscitation (CPR) has been one of the most paradigm-changing developments in modern medicine. Rooted in historical anatomic observations and developed into comprehensive cardiac care standards since the 1960s, CPR has become ingrained in medical training at all levels: from first responders to physicians, it is likely that almost everyone reading this has received formal training in CPR. Widespread modern CPR education is responsible for survival to hospital discharge in up to 30% of witnessed out-of-hospital cardiac arrest related to ventricular tachycardia or fibrillation, and outcomes have shown steady improvement over the last 10 years [1].

In contrast, the prognosis for cardiac arrest due to trauma is dismal. Even in the modern era of advanced trauma life support (ATLS), resuscitative thoracotomy, internal cardiac massage, and

* Corresponding author. University of Pittsburgh Medical Center, Suite F1271.1 PUH 200 Lothrop Street, Pittsburgh, PA 15213, USA.
E-mail address: kutcherme@upmc.edu (M.E. Kutcher).

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aortic cross-clamping, overall survival remains less than 10% [2], and has shown little improvement since the original development of these strategies in the 1960s [3]. Based on a survey of wartime injuries in 1984, Bellamy noted that many combat fatalities occurred as a result of injuries that, given adequate time, might otherwise have been technically reparable [4]. After cardiac arrest and cessation of blood flow, however, the brain begins to sustain permanent damage after 5 min [5] and the heart after 20 min [6]; even under the most ideal of circumstances, this window is near impossibly short to obtain surgical hemostasis in a bleeding patient. Furthermore, unlike non-traumatic cardiac arrest, external chest compressions do not effectively augment perfusion in an exsanguinated patient. Consequently, a novel approach to prolong survival from time of injury to surgical hemostasis is sorely needed.

Hypothermia has long been known to extend the window of organ viability and overall survival [7], a fact that cardiac surgeons and neurosurgeons use to their advantage daily. Conceptually, hypothermia suppresses metabolism, minimizes oxygen demand, and extends systemic tolerance to ischemia, even when induced after ischemia has already occurred [8]. Techniques for the controlled induction of hypothermia have been developed in animal models, where hypothermia can be induced within minutes and tolerated for up to 3 h without significant neurological sequelae [9]. Surgeons racing to control a major vascular injury in a dying patient are often outpaced by the speed of exsanguination and physiologic decline; if rapid induction of hypothermia could provide more time, however, otherwise lethal injuries could be repaired. This approach is the basis for emergency preservation and resuscitation (EPR) techniques for cardiac arrest from trauma.

2. Animal studies

Beginning in the late 1980s, Tisherman, Safar, and their Pittsburgh research group developed a canine model of hemorrhagic shock to investigate induction and reversal of hypothermia using peripherally-cannulated cardiopulmonary bypass (CPB) [10]. These key early studies culminated with the demonstration that, after up to an hour of normothermic hemorrhagic shock, hypothermia and circulatory arrest could safely be induced and reversed with no neurological impairment or histological evidence of brain damage [11]. Because formal CPB is complex and time-consuming, the model used a modified bypass with intra-aortic retrograde flushing of ice-cold saline, and venous drainage via a right atrial cannula placed through the internal jugular vein. Early work by Woods et al. showed that delivery of a 500 mL 4 °C saline bolus via an 8-French balloon-tipped femoral artery cannula into the descending thoracic aorta can rapidly cool the heart and brain in a canine model of exsanguinating injury, providing rapid neuroprotective hypothermia for up to 15 min of circulatory arrest as a bridge to formal bypass cannulation for resuscitation [12]. Early studies were limited by hind leg weakness suggesting spinal cord ischemia with durations of circulatory arrest longer than 15 min [13], but subsequent work has optimized the EPR approach with larger flush volumes into the distal abdominal aorta, achieving lower brain temperatures (10 °C) and allowing acceptable neurological outcomes in experimental animals after up to 120 min of arrest [14].

Building on this work, Rhee developed a swine model of EPR based on existing trauma techniques. For efficient aortic access, resuscitative thoracotomy is already the standard of care for patients presenting with traumatic arrest who meet criteria based on injury mechanism, presenting rhythm, and duration of arrest, or who develop profound refractory shock after injury [15]. In Rhee's animal model, left thoracotomy was performed, and the descending aorta clamped, cannulated, and flushed with a specially-designed cold preservation solution (Hypothermosol [Bio Life Technologies, Rockville, MD]) to initiate cooling and induce arrest, followed by formal aortic root and atrial cannulation for cardiopulmonary bypass [16]. This technique achieved intracranial temperatures of <10 °C within 12 min, allowing a 90-minute period of acellular hypothermic low-flow CPB at the end of which the descending aorta was repaired. All five experimental animals survived, with only one sustaining identifiable neurological injury. Using this model, Alam and others have systematically investigated the cooling and rewarming process, identifying a target tympanic membrane temperature of 10 °C (as opposed to 5 or 15 °C) [17,18], rapid hypothermia induction (2 °C/min) [19], and gradual rewarming (0.5 °C/min) [20] as optimal parameters to achieve good neurological outcome. Based on these studies the upper limit for duration of cardiac arrest and low-flow CPB without impairment of postoperative learning and memory appears to be 60 min [21,22]. Using these parameters in a clinically relevant porcine model of complex vascular, splenic, and colon injuries repaired during 1 h of EPR achieved a six-week neurologically intact survival rate greater than 75% [24]. The Pittsburgh group also created a canine model of prolonged hemorrhagic shock through catheter-controlled hemorrhage and uncontrolled bleeding from splenic injury leading to cardiac arrest at ~2 h, in which 85% survival was achieved with 1 h of post-arrest EPR; no animal treated with fluid resuscitation and external chest compressions alone survived [23]. They also found that adding a period of post-resuscitation mild hypothermia (34 °C) improved neurologic outcomes.

3. Clinical studies

There is one study of therapeutic hypothermia for traumatic cardiac arrest in humans currently in progress. The Emergency Preservation and Resuscitation for Cardiac Arrest from Trauma study (EPR-CAT; ClinicalTrials.gov identifier NCT01042015) is a feasibility and safety study of the induction of acellular hypothermic circulatory arrest for traumatic cardiac arrest after penetrating injury, initiated in 2014 with funding by the Department of Defense. Subjects are eligible if they are 18–65 years old, had signs of life in the field, and suffered a cardiac arrest from penetrating trauma within 5 min of hospital arrival or during evaluation in the Emergency Department. Exclusion criteria include significant multisystem trauma, obvious non-survivable injury, asystole as the presenting cardiac rhythm, suspicion of significant traumatic brain injury, pregnancy, and prisoner status. Subjects undergo routine care including airway management, fluid resuscitation, and resuscitative thoracotomy with clamping of the descending aorta. If a pulse is not restored, they may be entered into the trial. The descending thoracic aorta is cannulated using the Seldinger technique, and cooling to a tympanic membrane temperature of <10 °C via large-volume, retrograde aortic flushing with ice-cold saline is initiated. Surgical hemostasis is then achieved using standard damage control techniques, and the patient is rewarmed and reperfused using CPB. As a feasibility trial, the goal is to have a small number of trained and motivated surgeons involved rather than expecting all surgeons at a particular site to initiate EPR.

The primary outcome measure is survival to hospital discharge without major disability, defined as a Glasgow Outcome Scale-Extended of >5, compared to concurrent controls undergoing standard-of-care resuscitation by non-EPR-trained surgeons. Goal enrollment for the trial is 20 patients (10 EPR, 10 control), with potential for then refining the selection criteria or technique for another 20 patients. Currently, two Level 1 trauma centers in the United States are participating: the University of Maryland and the University of Pittsburgh.