Hot or cold? In support of cold

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Two recent studies (Bernard et al, 2002; Hypothermia After Cardiac Arrest (HACA) Study Group, 2002) demonstrated that mild hypothermia (32–34°C) improves survival and neurological outcome following cardiac arrest, leading to recommendations that comatose survivors of resuscitation from cardiac arrest should be cooled to 32–34°C for 12–24 hours (Nolan et al, 2003).

Is there a role for therapeutic mild hypothermia for the patient in traumatic haemorrhagic shock? This question has stirred up considerable controversy as clinical studies suggest detrimental effects while laboratory studies suggest benefit.

To discuss therapeutic hypothermia, the temperature levels should be defined. For this review, mild hypothermia is defined as 32–36°C, moderate as 28–32°C, deep as 10–20°C, profound as 5–10°C and ultraprofound as <5°C.

This review will discuss two scenarios for dying from severe haemorrhage for which hypothermia could have a therapeutic role. First, for patients with prolonged, uncontrolled haemorrhage, limited fluid resuscitation plus mild hypothermia and, perhaps, pharmacological hibernation, hypothermia could allow maintenance of a pulse until delayed resuscitation can be performed. Second, for patients with exsanguinating haemorrhage leading to cardiac arrest, pharmacological preservation (suspended animation) could allow a period of circulatory arrest to gain time for delayed resuscitation and resuscitative surgery.

CLINICAL STUDIES OF TRAUMA AND HYPOTHERMIA

Retrospective clinical studies (Jurkovich et al, 1987) have found an association between increased injury severity scores, decreased temperature and increased mortality. It is not clear, however, whether the hypothermia itself leads to the increase in mortality or if hypothermia is just another marker of severe injury.

The only randomized controlled trial related to hypothermia after trauma was a study conducted by Gentilello et al (1997). Hypothermic trauma patients were randomized to standard rewarming *vs* continuous arteriovenous rewarming. Patients in the continuous arteriovenous rewarming group required less fluid for resuscitation, but there was no difference in organ system failures or survival.

It is critical to recognize that the physiology of uncontrolled, exposure hypothermia, which occurs in trauma patients, is much different from that of controlled, therapeutic hypothermia with prevention of shivering and sympathetic discharge.

LABORATORY STUDIES

Hypothermia during haemorrhagic shock has been shown to have beneficial effects in multiple laboratory studies. For example, Prueckner et al (2001) showed that prolonged hypothermia for 12 hours, improved survival, compared to normothermia, after pressure-controlled haemorrhagic shock. Hypothermia for 1 hour was not as effective.

Because trauma patients frequently become hypothermic, a better clinical question may be whether or not to actively warm them. After prolonged, pressure-controlled haemorrhagic shock with spontaneous cooling to 35°C, Wu et al (2003) found that continued hypothermia significantly increased survival time.

Two clinically relevant questions remain: Does mild hypothermia cause coagulopathy? Does hypothermia improve outcome with realistic trauma and intensive care?

In pigs during haemorrhagic shock, Wu et al (2001) found that mild hypothermia did not alter coagulation tests and did not increase the early bleeding from a liver injury. After 1 hour, there was a tendency toward increased bleeding in the hypothermic group. Heparinized animals bled much more briskly than the other animals and died quickly.

In a large animal model with volume-controlled haemorrhagic shock, clinically relevant trauma by splenic injury and intensive-care life support, Wu et al (2004) found that mild hypothermia induced with surface cooling and infusion of room-temperature saline improved survival compared to normothermia. Hypothermia induction with ice-cold fluid was not effective possibly because of increased

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vasoconstriction or decreased fluid resuscitation requirements.

SUSPENDED ANIMATION

Current resuscitation strategies for the exsanguinating trauma victim, including emergency department thoracotomy, are usually doomed to failure. Vietnam War data suggests that some soldiers died of exsanguination in the first 5–30 minutes, often with injuries that could be repaired if the victim could have been kept alive. Dr Peter Safar and Colonel Ron Bellamy felt that a new approach, suspended animation, may represent a novel resuscitation strategy that can provide 'protection and preservation of the organism during clinical death of 2 hours or longer for transportation and controlled bleeding during pulselessness followed by delayed resuscitation' (Bellamy et al, 1996).

Suspended animation has been studied extensively in dogs at the Safar Center for Resuscitation Research with light anaesthesia and clinically relevant monitoring. Closed-chest cardiopulmonary bypass was used for induction of, and resuscitation from, suspended animation in the first studies. These studies found that 60 minutes of suspended animation was safe, but 120 minutes lead to brain damage. Profound hypothermia (<10°C) was better than deep (15°C). The University of Wisconsin solution, which is used for organ preservation for transplantation, did not provide any benefit. Use of a heparin-bonded bypass system and no systemic heparin was safe.

The most important of these initial studies, by Capone et al (1996), demonstrated that 1 hour of haemorrhagic shock followed by 1 hour of profound hypothermic circulatory arrest could allow recovery with normal neurological function and brain histopathology.

Since cardiopulmonary bypass cannot be taken outside of the hospital yet, a new strategy for induction of suspended animation by just using a large bore cannula advanced into the thoracic aorta has been explored in a model with rapid exsanguination to cardiac arrest, with the arrest assured by induction of ventricular fibrillation, and resuscitation with bypass. Periods of arrest of 15–120 minutes have been studied (Behringer et al, 2003). With increasing duration of arrest, more fluid was needed to achieve a brain temperature low enough to allow normal neurological outcome. In multiple small series of experiments, pharmacological approaches have not been beneficial, except for the antioxidant, tempol. Specialized fluids have shown some promise. For example, Unisol (Organ Recovery Systems, Inc., Charleston, SC) seems to be effective in studies by Rhee and colleagues (Alam et al, 2002) in a clinically relevant pig model of suspended animation.

When significant trauma (thoracotomy, laparotomy, splenectomy) was added to the model, animals often developed multiple organ system dysfunction (Nozari et al, 2004). Fortunately, brain histopathology can still be normal. Plasma exchange may help alleviate the organ system dysfunction and improve cerebral outcome.

CLINICAL TRIALS

Clinical trials for both mild hypothermia during haemorrhagic shock and profound hypothermic flush for exsanguinating haemorrhage are indicated. For haemorrhagic shock, it seems reasonable to start with a small feasibility and safety study. For suspended animation, given the current dismal prognosis, trials in patients who fail conventional resuscitative efforts could begin with available equipment. Looking toward the future, it will be important to develop better cannulation devices and techniques, including new guidance systems for vessel puncture and self-sealing catheters. Miniaturized cooling devices and pumps will also be needed.

CONCLUSIONS

Mild hypothermia during haemorrhagic shock is beneficial in animal models. Its effect clinically is yet to be determined. Clinical feasibility and safety trials are indicated, potentially followed by randomized controlled clinical trials.

Suspended animation appears to offer a novel approach to the management of the exsanguinating trauma patient who currently has almost no hope of survival. Clinical trials in selected trauma centres could be initiated using currently available materials. Development of novel cannulas, cannulation techniques and cooling devices should continue. It is reasonable to believe that the medic of the future could carry a smart catheter, cooling device, miniaturized pump and fluids needed for induction of suspended animation in the field.

These hypothermic strategies could become important parts of our armamentarium for management of the severely injured trauma victim in both civilian and military situations. HM

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KEY POINTS

- Clinical studies suggest that hypothermia is detrimental to trauma patients.
- Laboratory studies consistently show that mild hypothermia improves survival after haemorrhagic shock
- Suspended animation induced with profound hypothermia can allow a safe period of circulatory arrest for 90 minutes and, perhaps, for 120 minutes.
- More studies are needed to develop better pharmacological strategies and fluids to improve outcome from suspended animation.
- Clinical trials of mild hypothermia for prolonged haemorrhagic shock and suspended animation for exsanguination cardiac arrest are indicated.
- To facilitate application of resuscitative hypothermia in trauma patients, better cannulation techniques, self-sealing cannulas, and miniaturized cooling devices and pumps need to be developed.