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The Use of Pre-Hospital Mild Hypothermia after Resuscitation from Out-of-Hospital Cardiac Arrest

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Abstract

Hypothermia has emerged as a potent neuroprotective modality following resuscitation from cardiac arrest. Although delayed hospital cooling has been demonstrated to improve outcome after cardiac arrest, in-field cooling begun immediately following the return of spontaneous circulation may be more beneficial. Cooling in the field following resuscitation, however, presents new challenges, in that the cooling method has to be portable, safe, and effective. Rapid infusion of intravenous fluid at 4°C, the use of a cooling helmet, and cooling plates have all been proposed as methods for field cooling, and are all in various stages of clinical and animal testing. Whether field cooling will improve survival and neurologic outcome remains an important unanswered clinical question.

Key words: cardiac arrest; hypothermia; pre-hospital

Introduction

Cardiac arrest is common and causes substantial morbidity and mortality. The incidence of out-of-hospital cardiac arrest ranges from 0.04–0.13% of the total population per year (Becker et al., 1993; de Vreede-Swagemakers et al., 1997; Cobb et al., 2002). Despite advances in prevention and treatment including external chest compression with ventilation, defibrillation, and advanced life support, most patients paramedics resuscitate remain unconscious in the field. Survival with good neurologic recovery can be achieved in only 11–48% of resuscitated patients, and the balance either die during their hospital stay, or remain alive with severe neurologic deficits (Becker et al., 1993; de Vreede-Swagemakers *et al.*, 1997). Brain-specific strategies that go beyond prevention of cardiac arrest and limitation of the brain insult with effective CPR are needed.

Rationale for the Use of Hypothermia in Cardiac Arrest

Induced hypothermia was used in humans in the 1950s to protect the brain, initially during cardiac surgery, and subsequently after cardiac arrest (Bigelow et al., 1950; Williams and Spencer, 1958; Benson et al., 1959). Because of hemodynamic and respiratory problems with moderate hypothermia (28–32°C), these early protocols were abandoned. Interest in the use of very mild hypothermia was renewed following a study by Busto et al., which demonstrated that lowering the cerebral temperature a few degrees provided marked cerebral protection in a rodent model of ischemia (Busto et al., 1987). In the late 1980s, the application of mild hypothermia was shown to be beneficial in an animal model of cardiac arrest, renewing interest in the use of mild hypothermia in cardiac arrest patients (Leonov et al., 1990; Sterz et al., 1991). Several pilot trials of mild hypothermia in the late 1990s found improved neurologic function compared with historic controls (Bernard et al., 1997; Yanagawa et al., 1998; Nagao et al., 2000; Zeiner et al., 2000). These studies set the stage for the two seminal randomized clinical trials (Bernard et al., 2002; Hypothermia after Cardiac Arrest Study Group, 2002). They both showed improved outcome after ventricular fibrillation with external cooling to 32–34°C. In one trial of 275 patients, external cooling with a specialized blanket did not begin until after hospitalization, at a median of 105 min after return of spontaneous circulation, and the target temperature was achieved at a median of 8 h (Hypothermia after Cardiac Arrest Study Group, 2002). Hypothermia was continued for 24 h with concomitant use of midazolam, fentanyl, and pancuronium. Cooling was associated with an increased percentage of patients discharged alive without severe neurologic deficits, from 39% to 55%, for an absolute difference of 16%. In the other trial of 77 patients, external cooling was initiated in the field with paramedics applying cold packs, and was continued in the hospital, and target temperatures were achieved 120 min after return of spontaneous circulation (Bernard et al., 2002). Hypothermia was continued for 12 h with concomitant use of midazolam and vecuronium. Again cooling was associated with an increased likelihood of discharge alive

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without severe neurologic deficits, from 26% to 49%, for an absolute difference of 23%.

Experience in patients whose initial rhythms were asystole or pulseless electrical activity is limited. In one study of 33 such patients, external cooling with a specialized helmet did not begin until after hospitalization, at a median of 102 min from return of spontaneous circulation, and the target temperature was achieved at a median of 180 min after initiation (Hachimi-Idrissi et al., 2001; Holzer et al., 2005). Hypothermia was continued for 4 h with concomitant use of midazolam, fentanyl, and pancuronium. Cooling was associated with a non-significantly increased percentage of patients discharged alive without severe neurologic deficits, from 0% to 19%, for an absolute difference of 19%. In a meta-analysis of these three studies, benefit was substantial despite delays in all of these studies in achieving the target temperature(Holzer et al., 2005). The estimated number needed to treat with cooling to yield one more person who would survive cardiac arrest without severe neurologic deficits was 6, with a 95% confidence interval of 4 and 13 people.

Based on this and other evidence, the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation recommended the use of therapeutic hypothermia after cardiac arrest when the initial rhythm is ventricular fibrillation (VF) (Nolan et al., 2003). Many questions remain including how soon after return of spontaneous circulation (ROSC) cooling should begin, how best to induce and maintain hypothermia, how long to maintain hypothermia, how best to perform rewarming, and whether patients whose initial rhythms are not VF will benefit from cooling.

Rationale for the Use of Early Hypothermia

In considering the optimal timing of mild hypothermia, several animal studies suggest that cooling earlier results in more protection than cooling later. In a recent study of cardiac arrest in mice, application of hypothermia (using cooling blankets) during CPR was shown to enhance outcome compared with its application after ROSC (Abella et al., 2004). In a dog model of VF arrest, early application of mild hypothermia with cold normal saline infusion during CPR enables intact survival; however, delay in the induction of mild hypothermia reduces its efficacy, which suggests that mild hypothermia should be applied as early as possible (Nozari et al., 2006). In another study, Kuboyama et al. demonstrated that mild hypothermia induced immediately after cardiac arrest improves cerebral function and morphologic outcome, whereas delays of 15 min in the initiation of cooling after reperfusion does not improve outcome (Kuboyama et al., 1993). These animal studies suggest that intra-arrest cooling or cooling within 15 min after ROSC offers the best chance for neurologic recovery. However, these animal studies must be evaluated in the context of clinical studies, which have demonstrated that even delayed cooling, which is started 4–8 h after resuscitation, is associated with improved survival and neurologic outcome (Bernard et al., 2002; Hypothermia after Cardiac Arrest Study Group, 2002). The optimal timing of the initiation of mild hypothermia still needs to be determined.

One of the challenges of testing such a hypothesis in humans rests in finding a simple and safe method for rapidly inducing hypothermia that paramedics can apply in the field to patients they resuscitate from cardiac arrest. Several non-invasive and invasive cooling strategies have been investigated for use in hospitalized out-of-hospital cardiac arrest patients; however, these methods may not be applicable for use in the field. Field cooling needs to be safe, portable, and easy to administer. Invasive strategies using cooling catheters rapidly achieve the goal temperature, but are impractical for field application since they are placed into the inferior vena cava. External cooling techniques have the advantage of being less invasive; however, most of them including cooling blankets or fluid pads depend on an external energy supply or external cooling unit, and are not practical for out-of-hospital use. Ice packs have been used (Bernard et al., 2002); however, wide application is limited due to slow induction times to temperatures $<34^{\circ}$C compared to other methods.

Many cooling methods that have been proposed for use in the field by paramedics, including 4°C intravenous fluid, metal cooling plates, and cooling helmets. The development of new cooling methods and technology to augment or improve cooling are currently underway, and are an area of commercial interest. We will primarily discuss the use of cold fluids, and briefly discuss the use of other surface cooling methods.

Infusion of cold fluid

The use of intravenous infusion of ice-cold fluids is appealing since it is portable and easy to administer in the field in patients resuscitated from out-of-hospital cardiac arrest, and was initially proposed by Stephen Bernard's group in 2003 (Bernard et al., 2003). Rajek et al. studied the use of 40 mL/kg of normal 4°C saline solution infused over 30 min into 9 anesthetized volunteers who received vecuronium, and demonstrated a mean temperature decrease of 2.5°C (Rajek et al., 2000) Similar results have been demonstrated in elective surgical volunteer patients; however, healthy volunteer surgical patients or young volunteers may not be representative of patients with out-of-hospital cardiac arrest. In all of these studies, neuromuscular blockade was used to augment the effects of infusing cold fluid.

Prior to administering cold fluid in the field, the use of cold fluid was initially tested in hospitalized resuscitated out-of-hospital cardiac arrest patients. Results from three studies, including one of our own group, have been remarkably consistent (Bernard et al., 2003; Kim et al., 2005; Kliegel et al., 2005). Patients have low temperatures on admission after resuscitation from out-of-hospital cardiac arrest (mean temperatures were 35.5°, 35.4°, and 35.6°C in these three studies, respectively), and temperatures decrease substantially after the infusion of ice-cold intravenous fluids (mean decreases of 1.7°, 1.7°, and 1.8°C in the same three studies, respectively). In two studies, the fluids were administered with a pressure bag over 20–30 min (Bernard et al., 2003; Kim et al., 2005). In two of the studies, lactated Ringer's solution at 4°C was infused (Bernard et al., 2003; Kliegel et al., 2005), while in the other, normal saline at 4°C was infused (Kim et al., 2005). In two studies the amount infused was 2 L (Kim et al., 2005; Kliegel et al., 2005), while in the other, the amount was 30 mL/kg (Bernard et al., 2003). All protocols included neuromuscular blockade induced by sedatives and relaxants. The infusions were well tolerated with no deterioration seen in clinical examinations, blood tests, and echocardiograms. In these patients, hypothermia in the target range of 32–34°C was

maintained for 12–24 h using cooling blankets or more complicated devices that allow easy control of temperature (Kim et al., 2005; Kliegel et al., 2005). In one study, an endovascular device was used (Kliegel et al., 2005), and in the other, an external cooling device was used (Kim et al., 2005).

Although these studies demonstrate the feasibility and safety of lowering temperatures rapidly via the intravenous infusion of ice-cold fluids initiated in the hospital, the feasibility and safety of paramedics initiating such treatments in the field, the effect of such early treatments on neurologic outcome, and the differences in effects seen between those whose initial rhythm is VF versus those with other types of arrhythmias remains unclear.

The use of cold fluid in a field pilot study

In a recent pilot study, our group in Seattle examined the safety, efficacy, and feasibility of using a rapid infusion of normal saline at 4°C by paramedics in the field following ROSC in 125 patients who suffered cardiac arrest from VF, asystole, or pulseless electrical activity (Kim et al., 2007). Sixty-three received a rapid infusion of up to 2 L of cold normal saline, resulting in a mean temperature decrease of $1.24^\circ \pm 1^\circ$C, with a mean hospital arrival temperature of 34.7°C, while the 62 patients not randomized to cooling experienced a mean temperature increase of $0.10^\circ \pm 0.94^\circ$C ($p < 0.0001$), with a mean hospital arrival temperature of 35.7°C. In-field cooling was not associated with adverse consequences in terms of blood pressure, heart rate, arterial oxygenation, evidence of pulmonary edema on initial chest x-ray, or re-arrest. Secondary endpoints of awakening and being discharged alive from the hospital trended toward improvement in VF patients randomized to in-field cooling, suggesting a potential benefit for early cooling in VF patients. Early field cooling in non-VF patients, however, was not associated with improved outcomes.

A larger clinical study has recently been started in Seattle/King County to determine whether field cooling is associated with improved survival and neurologic outcome (*Clinical trials.gov* NCT00391469) in resuscitated cardiac arrest patients. Another goal is to determine whether field cooling is beneficial in both VF and non-VF patients.

Additional considerations

The use of cold intravenous fluid for pre-hospital cooling requires additional training and equipment, such as portable refrigeration for cooling the intravenous fluid, and the ability to measure core body temperature in the field. In Seattle and King County, each of the paramedic units is equipped with a portable refrigerator capable of storing several 1-L bags of normal saline at 4°C. Paramedics are placing esophageal temperature probes (Acoustascope esophageal stethoscope with temperature sensor; Level One, Rockland, ME) after tracheal intubation in all resuscitated out-of-hospital cardiac arrest patients. Paramedics record temperatures using a portable temperature recorder (YSI Precision 4000 A Thermometer; YSI Corp., Dayton, OH), and other temperature recorders that are directly integrated into Advanced Life Support monitors have also been used (HeartStart MRx ALS Monitor; Philips Health Care, Andover, MA).

During our recent pilot field study, paramedics intravenously administered up to 2 L of normal saline at 4°C, pancuronium (0.1 mg/kg), and diazepam (1–2 mg). As in the prior pilot study of patients treated in-hospital (Kim et al., 2005), the use of pancuronium appears to augment the cooling effect of the infusion of cold fluid. Seattle Medic One paramedics already used intravenous pancuronium and diazepam in the field before this study, but not for this indication. Not all EMS personnel utilize these drugs routinely, and this could limit the applicability of this cooling protocol to other EMS personnel. The use of cold fluid alone is enough to lower body temperature in the field; however, in these patients, skeletal muscle relaxation would need to be administered upon arrival at the emergency department. Other pharmacologic approaches to augment cooling, especially to control shivering, need to be studied. One alternative approach could be the use of meperidine, which has been used in some in-hospital cooling protocols. In our pilot study, the saline was infused through a peripheral intravenous line, 18-gauge or larger, using a pressure bag inflated to 300 mm Hg. In our research protocol we did not adjust for body weight the amount of normal saline at 4°C infused.

External cooling devices for use in the pre-hospital setting

External cooling devices, such as cooling helmets or cooling plates, have also been proposed for use in the pre-hospital setting. The use of cooling helmets is an attractive alternative, and they have been used in an in-hospital cardiac arrest patient pilot study (Hachimi-Idrissi et al., 2001). The investigators used a helmet containing a solution of aqueous glycerol that was placed around the head and neck to induce cooling. Prior to application the helmet was kept in a refrigerator to maintain its temperature at −4°C. Using this device, cooling to 34°C took a median time of 180 min as measured by a bladder thermometer, and 60 min as measured by a tympanic thermometer.

In another study, lowering of brain temperature was achieved using a specialized cooling helmet on volunteers, achieving a local brain temperature decrease of 1.8°C after 1 h of helmet use (Wang et al., 2004). The main benefit of the helmet is that hypothermia is locally delivered to the brain, lessening the possibility of systemic side effects of hypothermia. These helmets were intended for treating stroke patients early in the field; however, they could easily also be used in cardiac arrest patients. Some of these devices also need to be kept at or below 4°C prior to use, and thus will require refrigeration units for the paramedic units.

Another external cooling device consists of multiple metal cooling plates (Emcools; Emergency Medical Cooling Systems Ag, Vienna, Austria), which are pre-cooled to −20°C until shortly before use. The efficacy of these cooling plates has been demonstrated in a swine model of cardiac arrest (Bayegan et al., 2008). The main advantage of these cooling plates is the very rapid cooling rates possible compared to infusion of cold fluids. The cooling plates are also less invasive, since an infusion of fluid is not needed. In this animal model, no evidence of skin trauma was detected after the application of the metal cooling plates.

Cooling during resuscitation

In experimental cardiac arrest studies, intra-arrest cooling has been shown to improve resuscitation outcomes (Abella *et al.*, 2004), and in one study infusion of cold fluid at 4°C

during experimental CPR was shown to be feasible and to improve outcomes in a swine model of cardiac arrest (Nordmark and Rubertsson, 2005). These animal studies have led to the hypothesis that induction of hypothermia during the initial resuscitation phase may lead to better outcomes. The clinical feasibility of using cold fluid during resuscitation was recently demonstrated in a small pilot study of 5 patients. Paramedics infused Ringer's solution at 4°C intravenously at a maximum rate of 33 mL/min for a target temperature of 33°C, with a mean volume of 14 mL/kg, which resulted in a temperature decrease of 2.5°C (Kamarainen et al., 2008), these findings suggest that small volumes of fluid can rapidly reduce nasopharyngeal temperatures. Additional studies are needed to determine whether field cooling during resuscitation prior to ROSC improves outcomes.

Pre-hospital cooling is currently being used by a few EMS organizations in non-clinical trial settings. A recent survey of EMS physicians (Suffoletto et al., 2008) found that a few EMS groups have been using a combination of cold IV fluid and ice bags. The median duration of experience with these protocols was 12 months. One group from Wake Forest has published its experience using cold IV fluid (Myers and Lewis, 2007).

The use of pre-hospital hypothermia is still rare, as evidenced by a recent survey of emergency medical service physicians (Suffoletto et al., 2008), that found that only 9/145 surveyed physicians stated that they were associated with an EMS agency that uses a pre-hospital cooling protocol, which included either ice bags or cold IV fluid. Common perceived barriers include short transport times, lack of refrigeration equipment, and the receiving hospital's failure to continue hypothermia. A significant percentage of respondents also believed that the lack of guidelines for the use of pre-hospital hypothermia have hindered its implementation. Thus, pre-hospital hypothermia remains of unproven clinical benefit, particularly in relation to current recommendations for cooling hospitalized cardiac arrest patients; however, further studies are needed to examine the relative benefit of pre-hospital cooling for the long-term outcomes of patients resuscitated from cardiac arrest.

Conclusions

Experimental animal work demonstrates that early cooling after ROSC, or even intra-arrest cooling, offers the best chance or neurologic recovery following sudden cardiac arrest. Since the majority of cardiac arrests occur outside of the hospital, the application of therapeutic hypothermia presents numerous challenges. The use of intravenous fluid at 4°C has been shown to be safe for use in the field by paramedics, while the use of other techniques such as cold metal plates and helmets awaits further testing. Whether field cooling improves neurologic outcome and survival in resuscitated cardiac arrest patients needs to be determined by a large clinical trial.

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