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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 neuroprotectant following resuscitation from cardiac arrest. Although delayed hospital cooling has been demonstrated to improve outcome after cardiac arrest, in-field cooling started immediately following return of spontaneous circulation may be more beneficial. Cooling in the field following resuscitation, however, provides new challenges in that the cooling method has to portable, safe, and effective. Rapid infusion of 4 °C intravenous fluid, 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.

Keywords

Cardiac arrest; hypothermia; pre-hospital

Introduction

Cardiac arrest occurs commonly, causing substantial morbidity and mortality. The incidence of out-of-hospital cardiac arrest ranges from 0.04 to 0.13% of the total population per year (1–3). Despite advances in prevention and treatments including external chest compression with ventilation, defibrillation and advanced life support, most patients whom paramedics resuscitate remain unconscious in the field. Survival with good neurologic recovery can be achieved in only 11–48% of resuscitated patients, the balance either die during their hospital stay or remain alive with severe neurologic deficits(1,2). 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 1950's to protect the brain initially during cardiac surgery and subsequently after cardiac arrest (4–6). Because of hemodynamic and respiratory problems with moderate hypothermia (28–32°C), these early protocols were abandoned. In the late 1980's, the application of mild hypothermia (32–34°C) was shown to be beneficial in an animal model of cardiac arrest, add ref renewing interest in the use of mild hypothermia in cardiac arrest patients. Several pilot trials of mild hypothermia in the late 1990's found improved neurologic function compared with historic controls (7–10). These studies set the stage for the two seminal randomized clinical trials reported (11,12). They both showed

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improved outcome after ventricular fibrillation with external cooling to 32 to 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 minutes from return of spontaneous circulation, and the target temperature was achieved at a median of 8 hours(11). Hypothermia was continued for 24 hours with concomitant use of midazolam, fentanyl, and pancuronium. Cooling was associated with an increased percent 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 continued in the hospital, and target temperature was achieved by about 120 minutes after return of spontaneous circulation(12). Hypothermia was continued for 12 hours with concomitant use of midazolam and vecuronium. Again cooling was associated with an increased likelihood of discharge alive 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 minutes from return of spontaneous circulation, and the target temperature was achieved at a median of 180 minutes after initiation (13,14). Hypothermia was continued for 4 hours with concomitant use of midazolam, fentanyl, and pancuronium. Cooling was associated with a non-significant increased percent 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 each of these studies in achieving the target temperature(14). The estimated number needed to treat with cooling to yield one more person who would survive cardiac arrest without severe neurologic deficits was six with a 95% confidence interval of 4 to 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 where the initial rhythm is ventricular fibrillation(15). 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 ventricular fibrillation 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(16). 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 suggest that mild hypothermia should be applied as early as possible(17). In another study, Kuboyama 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(18). 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(11,12). 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

whom 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 are rapid in achieving goal temperature, however, are impractical for field application since these catheters 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. The use of ice packs have been used(12), however, wide application is limited due to slow induction time to temperatures of less than 34 °C compared to other methods.

Many cooling methods which have been proposed for use in the field by paramedics: the use of cold 4°C intravenous fluid, the use of cold metal cooling plates, and the use of a cooling helmet. The development of new cooling methods and technology to augment or improve cooling are currently under way and are an area of commercial interest. We will mainly discuss the use of cold fluid 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(19). Rajek studied the use of 40 ml/kg of normal 4°C saline solution over 30 min in 9 anesthetized volunteers who received vecuronium and demonstrated a mean temperature decrease of 2.5° C. (20) Similar results have been demonstrated in elective surgical volunteer patients, however healthy volunteer surgical or young volunteers may not be applicable to 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(19,21,22). Patients have low temperatures on admission after resuscitation from out-of-hospital cardiac arrest (mean 35.5, 35.4, and 35.6°C in these three studies) and drop them drop substantially after the infusion of ice-cold intravenous fluids (1.7, 1.7, 1.8°C respectively). In two studies, the fluids were administered with a pressure bag over 20 to 30 minutes(19,21). In two studies, 4°C lactated Ringers solution was infused(19,22), while in the other, 4°C normal saline was infused(21). In two studies the amount infused was two liters(21,22), while in the other, it was 30 ml/kg (19). All protocols included paralytic agents and sedatives. The infusions were well tolerated without deterioration noted on clinical examination, blood tests, and echocardiograms. In these patients, hypothermia in the target range of 32 to 34°C was maintained for 12 to 24 hours using cooling blankets or more complicated devices that allow for easy control of temperature(21, 22). In one study, an endovascular device was used(22), and in the other, an external cooling device(21).

Although these studies demonstrate the feasibility and safety of lowering temperatures rapidly with 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 difference in effect between those whose initial rhythm is ventricular fibrillation or not remain unclear.

The use of cold fluid in the field-pilot study—In a recent pilot study, our group in Seattle examined the safety, efficacy, and feasibility of using a rapid infusion of 4°C normal saline by paramedics in the field following ROSC in 125 patients who suffered cardiac arrest from VF, asystole, or pulseless electrical activity(23). Sixty three received a rapid infusion of up to 2

liters of cold normal saline resulting in a mean temperature decrease of 1.24 ± 1°C with a hospital arrival temperature of 34.7°C, while the 62 patients not randomized to cooling experienced a mean temperature increase of 0.10 ± 0.94°C ($p<0.0001$) with a 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 for pulmonary edema on initial chest x-ray, or re-arrest. Secondary endpoints of awakening and discharged alive from 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 trial. 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 IV fluid for pre-hospital cooling requires additional training and equipment, such as portable refrigeration for cooling the intravenous fluid and ability to measure central body temperature in the field. In Seattle and King County, each of the paramedic units are equipped with portable refrigerators capable of storing several one-liter bags of normal saline at 4°C. Paramedics are placing esophageal temperature probes (Acoustascope Esophageal Stethoscope with temperature sensor, Level One, Rockland, Maine) 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 Corporation, Dayton, OH) and other temperature recorders which are directly integrated into the Advanced Life Support (ALS) monitors have been used (HeartStart MRx ALS Monitor, Philips Health Care).

During our recent pilot field study, paramedics administered intravenously up to two liters of 4°C normal saline, pancuronium (0.1 mg/kg), and diazepam (1–2 mg). As in the prior pilot study of patients treated in hospital(21), 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 utilize these drugs routinely and this could limit the applicability of this cooling protocol to other EMS. The use of cold fluid alone is enough to lower the temperature in the field, however, in these patients, skeletal muscle relaxation would need to be administered upon arrival at the emergency department. In our pilot study, the saline was infused through a peripheral intravenous line, 18-gauge or larger, using a pressure bag inflated to 300 mmHg. In our research protocol we did not adjust the amount of 4°C normal saline to body weight.

External cooling devices for the 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 has been used in an in-hospital cardiac arrest patients pilot study(13). The investigators used a helmet device containing a solution of aqueous glycerol and placed around the head and neck in order to induce cooling. Prior to application the helmet device was kept in the refrigerator to maintain temperature at −4 °C. Using this device, cooling to 34 °C took a median time of 180 min (as measured by bladder thermometer) and 60 min as measured by typmpanic thermometer.

In another study, lowering of brain temperature was achieved using a specialized cooling helmet in volunteers, achieving local brain temperature decrease of −1.8 °C after 1 hour of helmet use (24). 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 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 have been demonstrated in a swine model of cardiac arrest(25). The main advantage of these cooling plates is the very rapid cooling rates compared to infusion of cold fluid. 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(16) and in one study infusion of cold 4 °C fluid during experimental CPR was shown to be feasible and improve outcomes in a swine model of cardiac arrest(26). These animal studies have lead 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 4 °C Ringer's solution intravenously at a maximum rate of 33 ml/min for a target temperature goal of 33 °C with a mean volume of 14 ml/kg which resulted in a temperature decrease of 2.5 °C (27), these findings suggest that small volumes of fluid can rapidly reduce nasopharynal temperatures. Additional studies to determine whether field cooling during resuscitation prior to ROSC improves outcomes are needed.

The use of pre-hospital cooling is currently being used by a few emergency medical systems (EMS) in non-clinical trial settings. In a recent survey of EMS physicians(28) a few EMS have been using a combination of cold IV fluid or ice bags. The median duration of experience with a protocol was 12 months. One group from Wake Forest has published its experience with using cold IV fluid (29).

The use of pre-hospital hypothermia is still rare as evidenced by a recent survey of emergency medical services physicians(28), only (9/145) of 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 implementation. 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 in 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 arrest occur outside of the hospital, the application of therapeutic hypothermia present numerous challenges. The use of cold 4°C intravenous fluid 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 tested in a large clinical trial.

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