Abstract

Prolonged standard cardiopulmonary resuscitation (CPR) does not reliably sustain brain viability during cardiac arrest. Pre-hospital adjuncts to standard CPR are needed in order to improve outcomes. A preliminary dog study demonstrated that surface cooling of the head during arrest and CPR can achieve protective levels of brain hypothermia (30°C) within 10 minutes. We hypothesized that protective head-cooling during cardiac arrest and CPR improves neurological outcomes. Twelve dogs under light ketamine-benzothiopental anesthesia were arrested by transthoracic induction of ventricular fibrillation. The treated group consisted of six dogs whose shaven heads were moistened with saline and packed in ice immediately after confirmation of ventricular fibrillation. Six control dogs remained at room temperature. All 12 dogs were subjected to four minutes of ventricular fibrillation and 20 minutes of standard CPR. Spontaneous circulation was restored with drugs and countershocks. Intensive care was provided for five hours post-arrest and the animals were observed for 24 hours. In both groups, five of the six dogs had spontaneous circulation restored. After three hours, mean neurological deficit was significantly lower in the treated group (P=0.016, with head-cooled dogs averaging 37% and the normothermic dogs 62%). Two of the six head-cooled dogs survived 24 hours with neurological deficits of 9% and 0%, respectively. None of the control group dogs survived 24 hours. We concluded that head-cooling attenuates brain injury during cardiac arrest with prolonged CPR. We review the literature related to the use of hypothermia following cardiac arrest and discuss some promising approaches for the pre-hospital setting.

Introduction

More than 340,000 Americans die each year of coronary heart disease in the pre-hospital setting. In addition, there are a large number of patients who sustain permanent neurological damage following successful resuscitation from cardiac arrest. Adjuncts to cardiopulmonary resuscitation (CPR) are needed to improve the neurological outcome of these patients. Application of protective therapy prior to restoration of circulation, such as hypothermia, may prevent the post-ischemic encephalopathy that follows cardiac arrest. One of the most important mechanisms by which therapeutic hypothermia prevents further damage to the brain is by decreasing the oxygen demand of cerebral tissue.

Hypothermia, whether intentional or by accident, has long been known to prevent brain damage during cardiac arrest. Hypothermia has also been employed after return of spontaneous circulation with some encouraging results. Instead of allowing hypothermia to become established in only these rare patients, it was proposed that the application of hypothermia be examined as a protective tool during “routine” cardiac arrest. This study, completed in 1984, compared cardiac and cerebral resuscitability of normothermic versus head-cooled dogs subjected to a prolonged CPR insult. The authors hypothesized that protective head-cooling during cardiac arrest and CPR achieves protective levels of brain hypothermia and results in improved neurological outcomes.

This study was conducted initially in the early 1980s and published as an abstract in 1985. From the 1990s to the present there has been a regained interest in the topic with a flourishing of publications related to the topic. The result has been organizations such as the Canadian Resuscitation Council and the Canadian Association of Emergency Physicians releasing position statements advocating head-cooling for patients who present with non-perfusing ventricular fibrillation or ventricular tachycardia and are resuscitated to hemodynamic stability yet remain unresponsive. The optimal method of achieving cooling is still unclear, with multiple methods being applied. The data from this study, conducted over two decades ago, is being published here for both historical value and because the data specifically on head-cooling during cardiac arrest may contribute to this ongoing discussion.

Materials and Methods

A series of pilot experiments was performed to investigate cooling rates of the brain at room temperature and with head-cooling. The formal experimental study was set up to investigate the role of head-cooling initiated at the onset of witnessed pre-hospital cardiac arrest. The experimental protocol was designed to replicate a witnessed cardiac arrest, with four minutes of ventricular fibrillation (VF), 20 minutes of basic life support (BLS), followed by advanced cardiac life support (ACLS). This study was approved by the institutional review board, and the Animal Care and Use Committee of the Allegheny-Singer Research Institute.

Pilot study

Several pilot experiments were performed to investigate the feasibility of achieving protective levels of brain hypothermia with ten minutes of cardiac arrest, utilizing head surface cooling. Three dogs were prepared in a similar fashion to the formal study with the exception of having temperature probes, insulated and sealed with bone wax, placed in the cardiac portion of the esophagus, below the galea, in the rectum, and one centimeter into the right frонтопарietal cerebral cortex. After transthoracic electrical induction of VF, Dog #1 was allowed to cool undisturbed, with no CPR and no head-cooling; at room temperature, Dog #2 was head-cooled after induction of VF but had no CPR performed, and Dog #3 was head-cooled while CPR was administered for VF by a Michigan Instruments “thumper.” A fourth undisturbed pilot study was performed with a prototype cooling device (NH₃NO₃ – H₂O; cold pack technology) and with probes in the thalamic, subcortical, and subgaleal regions.
Experimental study

Twelve healthy flat-chested mongrel dogs weighing 12.25 kg were fasted overnight with water ad lib. All dogs were premedicated with ketamine (10 mg/kg IM) and anesthetized with halothane (0.75-4.0%), nitrous oxide (50%), and oxygen (50%). Endotracheal intubation was performed with a cuffed tube when anesthesia reached sufficient depth. Pre-insult rectal and cardiac temperatures were maintained at 37-38°C. Infra-diaphragmatic aortic catheters and Swan-Ganz catheters with temperature probes were placed by femoral cutdown. All dogs had their heads shaved. The level of anesthesia was allowed to lighten by allowing all dogs to spontaneously breathe room air for 4-6 min. VF was induced transthoracically with 100 volts alternating current for 3 sec. Upon confirmation of VF, six dogs were cooled by having bags of ice placed around their heads. All dogs were subjected to 4 min ventricular fibrillation and 20 min “controlled” CPR. Sixty chest compressions per minute and one interposed ventilation (TV=25 mL/kg, F10 1.0) per five compressions were delivered using a Michigan Instruments “thumper.” Initial systolic blood pressure during CPR was maximized but not allowed to exceed 70 mmHg. Initial chest compression was limited to two inches after 1.2 min manual CPR to loosen the chest. Sandbags were used to stabilize the chest laterally. If systolic blood pressure was not maintained above 30 mmHg after 10 min CPR, the animal was excluded. Restoration of total spontaneous circulation (ROSC) was achieved using the 1984 ACLS protocol (Figure 1) and the total number of ACLS steps was calculated. Mean arterial pressure was maintained above 60 mmHg using a continuous epinephrine infusion and fluid administration titrated by pulmonary artery pressure and/or central venous pressure. Following ROSC, the ice bags were removed from the head and warming was achieved by heating pads applied to the body but not to the cold, wet head. One hour after ROSC, the weaning process was begun. All dogs received 4-5 hr intensive care. Then they were returned to their cages with supplemental oxygen and maintenance IVs. Neurological deficit scores (NDS) were obtained at 3, 12, and 24 hr post-resuscitation. A slightly modified version of the neurological scoring system of the Resuscitation Research Center was employed to assess neurological outcome (Figure 2). An NDS of 100% represented brain death. No neurological scoring was performed when cardiopulmonary decline prevented adequate neurological testing (Figure 3).

Data were analyzed using the Student’s two-tailed t-test for independent means, unless otherwise referenced.

Results

Pilot study

In the pilot studies, therapeutic levels of core-temperatures were reached within 10 minutes (<32°C) in head-cooled dogs (ice) whether CPR was applied or not (Figure 4A). Extremely hypothermic subgaleal temperatures (26°C) were achieved within 10 minutes in instrumented animals with an ice pack technology (ammonium nitrate) cooling device (Figure 4B).

Experimental study

Six preliminary trials of the experimental study were initially carried out to formalize the protocol. All of the following 12 animals that were fibrillated were able to achieve ROSC and met inclusion criteria. Head-cooled dogs had significantly better neurological outcomes than control dogs (P=0.016). Mean NDS for head-cooled dogs at three hours was 37.2% while mean NDS for control dogs was 61.8%. Two head-cooled dogs survived 24 hours. One was neurologically intact while the other had an NDS of 9%. No control dogs survived 24 hours. One control dog had life support terminated after brain death, as defined by NDS (Figure 2), at 18 hours. With the exception of the previously mentioned dog, all dogs who failed to survive 24 hours died of cardiopulmonary causes.

In spite of statistically significantly lower core temperatures at the time of defibrillation (P=0.04; one-tailed t-test), head-cooled dogs had the same ease of cardiac resuscitation. In addition, mean ACLS steps required to restore spontaneous circulation was not significantly different between head-cooled and control dogs (P=0.713; 5 vs. 5.7 ACLS steps, respectively). In both groups, five of the six dogs had successful ROSC. Mean arterial pressure obtained during CPR was not significantly different (P=0.262) between head-cooled (25.50 mmHg) and control (19.85 mmHg) groups.

In head-cooled dogs, core temperature became significantly lower than rectal temperature (P<0.001) one minute after ROSC and remained so (P=0.004) at five minutes after ROSC (Figure 5). The nadir of afterdrop, that is drop in cardiac temperature after ROSC, occurred one minute after ROSC and averaged 1.6°C with core temperature falling to 34.5°C. In control dogs, core and rectal temperatures never became significantly different (<0.25°C difference at 20 min of CPR). Rewarming was accomplished in one hour. There was no statistical difference in weight (P=0.442), core (P=0.619) and rectal (P=0.941) temperature, conjunctival oxygenation (P=0.945), and arterial pressure (P=0.968) between the groups at baseline.

Discussion

Cardiac arrest results in cerebral hypoperfusion with resultant global brain ischemia. In addition to the immediate damage caused by hypoxemia, there is a cascade of injuries...
induced by reperfusion. Reperfusion injuries are mediated by several mechanisms including protein synthesis inhibition, induction of proteases, and excitatory amino acid release.4

This study consisted of a dog model that simulated pre-hospital cardiac arrest with four minutes of down time prior to initiation of 20 minutes of standard CPR (BLS). Head-cooling was started at the onset of arrest and was continued during CPR, followed by ACLS. Head-cooled dogs had significantly better neurological outcomes than control dogs three hours after spontaneous return of circulation. These results have been bolstered further by several subsequent studies that reinforce the premise that there are benefits of induced hypothermia in cardiac arrest.9-12 Leonov, et al. also reported that mild hypothermia induced after the onset of cardiac arrest improves neurological performance, function, and overall brain morphology.7

While several mechanisms may play a role, head-cooled dogs demonstrated awareness at three hours post-arrest while no control dogs did. Although longer, more controlled post-resuscitation studies are needed, it is felt that the superior three-hour NDS of head-cooled dogs is a valid indication of cerebral protection and insult attenuation. It has also been postulated that profound subgaleal cooling may redirect blood flow from the external to the internal carotid system, thus improving the efficacy of CPR in generating blood flow to the brain.

Regional rates of cooling have been examined in a cold water drowning model in which canines were submerged in cold water with clamped endotracheal tubes. Rate of cortical cooling after arrest in this experiment was found to be comparable to the rate found in our feasibility study. Cortical temperatures were found to drop faster than cardiac temperatures, as would be expected if conduction were the dominant mechanism of cooling. No diving reflex was noted to occur.12 These findings suggest that conductive cooling may be sufficient to account for cerebral protection in cold water drowning. As in accidental and intentional hypothermia, mild afterdrop was found to occur in head-cooled dog resuscitations. Apparently afterdrop was not of sufficient magnitude to trigger rescue arrest as none was noted to occur.

A limitation of this study is the use of sodium bicarbonate as part of the ACLS protocol. These experiments were conducted originally in 1984, and at that time sodium bicarbonate was utilized in the ACLS protocol. However, there is some recent data suggesting sodium bicarbonate is beneficial in prolonged cardiac arrest.14 Researchers also could not be blinded as to which dogs were in the head-cooled group or the control group. Objective NDS scoring scales were used in an attempt to minimize scoring biases. In addition, the study could have benefited from longer observation periods and histological examination of the brain at autopsy.

Review of the literature

The therapeutic use of hypothermia was described as early as the times of the Egyptians, Greeks, and Romans.15 Napoleon’s surgeon-general reported that wounded soldiers placed closer to the fire died quicker than soldiers not warmed.16 In the modern era, therapeutic hypothermia was described in a series of case reports in 1958 by a surgeon who cooled patients (30-34°C) with signs of severe neurological injury after cardiac arrest. Three of these patients recovered completely while one had a moderate neurological deficit after recovery.17 Other case reports have described both intentional and unintentional hypothermia enabling patients to remain neurologically intact after one hour of total circulatory arrest in pediatric open heart surgery, after

Figure 2. Canine neurological deficit scoring.
forty minutes of submersion in cold water, and after three-and-a-half hours of external CPR.

The topic of therapeutic hypothermia in the treatment of cardiac arrest has regained interest in the late 1990s. In 1997, Bernard, et al. published a report in which they prospectively studied patients who suffered out-of-hospital cardiac arrest and remained unconscious after return of spontaneous circulation. They surface-cooled these patients in the ED and ICU for twelve hours and compared their neurological outcome with a control group of similar patients studied by retrospective chart review. They concluded that neurological outcome was significantly improved and mortality decreased in the mild hypothermic group with no increase in complications. A similar 1998 study by Yanagawa, et al. surface-cooled patients for 48 hours and demonstrated a trend, although not statistically significant, toward increased survivability with mild hypothermia. Their cooled patients had an increased incidence of pulmonary complications, but they theorized this was because of extended (five to six days) use of paralytic and sedative agents. In 2000, the Hypothermia After Cardiac Arrest (HACA) Study Group published a prospective study on the feasibility and safety of therapeutic hypothermia after cardiac arrest. They cooled patients in the ED after out-of-hospital cardiac arrest using head-cooling and external body cooling blankets, and maintained these patients in mild hypothermia for 24 hours, followed by passive rewarming. They concluded that these patients had a two-fold improvement in outcome as compared to historical normothermic controls, without increasing the incidence of sepsis, coagulopathy, neutropenia, or thrombocytopenia. Yanagawa, et al. suggested that even patients with out-of-hospital cardiac arrest and out-of-hospital ROSC without witnessed arrest, bystander CPR, or initial rhythm of ventricular asystole may benefit from induced hypothermia.

Although there is general agreement that mild hypothermia is most beneficial while deep hypothermia can be detrimental, different studies have used alternative methods that achieve hypothermia at different rates. Animal studies have shown that a fifteen minute delay in cooling can negate the beneficial effects of mild hypothermia. The HACA Study Group of 2000 took an average of 287 minutes to achieve adequate hypothermia, and the study by Feldberg, et al. required an average of 301 minutes to adequately cool patients, despite using both cooling blankets and iced gastric saline lavage. Feldberg and colleagues concluded that externally induced mild hypothermia is both slow and imprecise. Hachimi-Idrissi, et al. utilized a helmet device to achieve mild hypothermia post-ROSC in patients with cardiac arrest who remained

Neurological Deficit Scoring (NDS):

| Points | Scores % |
|--------|----------|
| Best   | Worst    | Best | Worst |
| 1) Level of Consciousness | 0 | 100 | 0 | 20 |
| 2) Respiration | 0 | 100 | 0 | 20 |
| 3) Cranial Nerve Function | 0 | 100 | 0 | 20 |
| 4) Motor and Sensory Function | 0 | 100 | 0 | 20 |
| 5) Behavior | 0 | 100 | 0 | 20 |
| TOTAL | 0 | 500 | 0 | 100% |

Figure 3. Neurological scoring system. Neurological deficit scoring carried out as per protocol, using modifications of the methods of Nemoto, et al. and Grisvold, et al. Clinical neurological results expressed as neurological deficit (ND) score in percent. ND 100% means brain death and 0% means normal.
unconscious after return of spontaneous circulation. They were able to achieve a tympanic temperature of 34°C in a median of sixty minutes while it took a median of 180 minutes to achieve mild core hypothermia.\(^\text{27}\) Nozari, et al. attained tympanic temperatures of 34°C after approximately 20 minutes utilizing venovenous shunt cooling in an animal model.\(^\text{28}\) Kim, et al. were able to rapidly reduce core temperature by 1.7°C in chemically paralyzed patients by rapid infusion of 2 L of 4°C normal saline.\(^\text{29}\)

The plethora of pilot and feasibility studies in the late 1990s and early 2000s led to two randomized controlled studies published in the New England Journal of Medicine in February 2002. The study by Bernard et al. compared moderate hypothermia to normothermia in patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest.\(^\text{30}\) Patients were randomized to normothermia or hypothermia based on day of the week, and hypothermic patients were cooled in the field and later in the ED using cold packs applied to the head and torso. They were maintained moderately hypothermic for twelve hours, and then were actively rewarmed starting at eighteen hours. The researchers concluded that moderate hypothermia for twelve hours after resuscitation resulted in a significant improvement in outcome, but not a significant improvement in mortality. Therapeutic hypothermia was not associated with clinically significant adverse effects.

The study by the HACA Study Group analyzed the use of mild hypothermia in improving neurological recovery after resuscitation from out-of-hospital cardiac arrest.\(^\text{31}\) Patients who met the inclusion criteria and were brought to a participating ED were randomized via a sealed envelope to either the mild hypothermia or control group. Patients in the mild hypothermia group were cooled using an external cooling device and maintained mildly hypothermic for twenty-four hours following passive re-warming. The patients in the mild hypothermic group had both a significant decreased mortality rate and improved neurological outcome as compared with standard life support. There was not a significant difference in complication rate between the groups, although there was a non-statistically significant higher incidence of sepsis in the hypothermic group.

**Recommendations**

Based on these promising studies, the ALS Task Force of the International Liaison Committee on Resuscitation (ILCOR) recommends that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm is ventricular fibrillation.\(^\text{32}\) Although they make no specific recommendation in terms of methodology to achieve mild hypothermia, a variety of cooling methods have been applied in the past. These include cooling blankets, direct application of ice, iced saline gastric lavage, venous cooling, and cooling during bypass. None of these methods has met the ideal criteria of ease of use in the field along with quickly reaching mildly hypothermic temperatures. There are several very promising cooling techniques for use in the pre-hospital setting: including ice packs (Figure 6), cooling helmets,\(^\text{33}\) and cold IV fluid infusion.\(^\text{33,34}\)

**Conclusions**

Cooling of the head is advantageous over systemic surface-cooling by limiting the drop in cardiac temperature prior to return of spontaneous circulation and its ease of application. Head-cooling can be applied clinically with a device employing cold pack technology that is portable, inexpensive, and applicable by laymen in the field. This study shows that head-cooling is a promising means of protecting the brain during CPR that does not have an adverse effect on cardiac resuscitation.

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