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Experimental paper

Intra-arrest selective brain cooling improves success of resuscitation in a porcine model of prolonged cardiac arrest☆

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ABSTRACT

Aims of study: We have previously demonstrated that early intra-nasal cooling improved post-resuscitation neurological outcomes. The present study utilizing a porcine model of prolonged cardiac arrest investigated the effects of intra-nasal cooling initiated at the *start* of cardiopulmonary resuscitation (CPR) on resuscitation success. Our hypothesis was that rapid nasal cooling initiated during "low-flow" improves return of spontaneous resuscitation (ROSC).
Methods: In 16 domestic male pigs weighing 40 ± 3 kg, VF was electrically induced and untreated for 15 min. Animals were randomized to either head cooling or control. CPR was initiated and continued for 5 min before defibrillation was attempted. Coincident with starting CPR, the hypothermic group was cooled with a RhinoChill™ device which produces evaporative cooling in the nasal cavity of pigs. No cooling was administrated to control animals. If ROSC was not achieved after defibrillation, CPR was resumed for 1 min prior to the next defibrillation attempt until either successful resuscitation or for a total of 15 min.
Main results: Seven of eight animals in the hypothermic group (87.5%) and two of eight animals in control group (25%) ($p = 0.04$) were successfully resuscitated. At ROSC, brain temperature was increased from baseline by 0.3 °C in the control group, and decreased by 0.1 °C in the hypothermic animals. Pulmonary artery temperature was above baseline in both groups.
Conclusion: Intra-nasal cooling initiated at the start of CPR significantly improves the success of resuscitation in a porcine model of prolonged cardiac arrest. This may have occurred by preventing brain hyperthermia.

1. Introduction

Sudden cardiac arrest (SCA) is a leading cause of death in the United States, Canada and Europe.[1–4] The annual incidence of SCA in North America is almost 0.55 per 1000 population[3,5] and about 700,000 patients in Europe.[4] Despite huge efforts to improve outcomes from sudden cardiac death, including reassessment and publication of new Cardiopulmonary Resuscitation Guidelines every 5–8 years for the past 3 decades, survival rate remains dismal.[6]

Systemic hypothermia initiated after resuscitation has been shown to improve survival and long-term neurologic outcome after cardiac arrest.[7–11] Based on data from two recent randomized clinical studies,[8,9] the most recent American Heart Association Guidelines of Cardiopulmonary Resuscitation (CPR) now stipulate that unconscious, adult patients successfully resuscitated from an out-of-hospital ventricular fibrillation (VF) cardiac arrest should be cooled to 32–34 °C for 12–24 h.[12]

In addition to neuroprotection, hypothermia has also been documented to improve CPR outcome. In a porcine cardiac arrest model, systemic hypothermia (30–35 °C) established before cardiac arrest improved the defibrillation success and resuscitation outcome suggesting hypothermia may be beneficial to the resuscitation efforts.[13] Intra-arrest systemic hypothermia has also been shown to reduce mortality rates in mice.[14] Furthermore, we have previously demonstrated in a porcine model that intra-nasal cooling initiated during CPR required fewer defibrillation shocks to achieve return of spontaneous circulation (ROSC) in the absence of

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systemic hypothermia[15] after 10 min of untreated VF. The mechanism remains unclear whether systemic or intra-nasal cooling benefits the resuscitative effort.

In the present study, we investigated the effect of intra-nasal cooling at the initiation of CPR on the success of resuscitation and its potential mechanisms. Our hypothesis was that rapid intra-nasal brain cooling during "low-flow" CPR following 15 min of untreated cardiac arrest would improve ROSC in a porcine model.

2. Methods

Experiments were performed on an established swine model of cardiac arrest and CPR.[15] All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH publication 86-32, 146 revised 1985). The protocol was approved by the Institutional Animal Care and Use Committee of the Weil Institute of Critical Care Medicine.

2.1. Animal preparation

Sixteen male domestic pigs weighing 40 ± 3 kg were fasted overnight except for free access to water. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and completed by ear vein injection of sodium pentobarbital (30 mg/kg). Additional doses of sodium pentobarbital (8 mg/kg) were injected intravenously to maintain anesthesia at intervals of 1 h. The animals were mechanically ventilated with a volume-controlled ventilator (Model MA-1, Puritan-Bennett, Carlsbad, CA). End-tidal PCO_2 ($ETCO_2$) was monitored with an infrared analyzer (Model 01R-7101A, Nihon Kohden Corp., Tokyo, Japan). Respiratory frequency was adjusted to maintain $ETCO_2$ between 35 and 40 mm Hg. Aortic pressure was measured using a fluid-filled catheter advanced from the right femoral artery into the thoracic aorta. Right atrial, pulmonary arterial pressure and blood temperature were measured using a 7-French thermodilution-tipped catheter positioned in the pulmonary artery. Electrocardiogram (ECG) signal was obtained using 3 adhesive electrodes applied to the shaved skin of the right upper, left upper and lower limbs. VF was induced using a 5-French pacing catheter (EP Technologies Inc., Mountain View, CA) advanced from the right cephalic vein into the right ventricle. The position of catheters was confirmed by characteristic pressure morphology and/or fluoroscopy. Once the initial anesthesia procedure was completed, the animal was turned over onto the prone position. A 0.5 cm diameter burr hole was made 1 cm lateral to the sagittal suture and 1 cm anterior to the parietal–occipital suture. A needle temperature sensor (NOVATEMP Myocardial Temperature Probes, NovaMed, LLC, New York, NY) was introduced through the burr hole to a depth of 4 cm to measure brain temperature. The animal was then returned to a supine position.

2.2. Experimental protocol

Fifteen min before inducing cardiac arrest, baseline measurements were obtained, intra-nasal cooling instruments were set up and animals were then randomized by the sealed envelope method to blind the surgical preparation team. The study could not be blinded after the start of CPR because of cooling, but all of the CPR was performed by the Thumper® device, a pneumatic piston-driven chest compressor (Model 1000, Michigan Instruments, Grand Rapids, MI), which was set up before cooling. Except for cooling, both groups of animals were treated identically. VF was induced by a 1 mA alternating current delivered to the right ventricular endocardium through the pacing catheter. Mechanical ventilation was discontinued after onset of VF. Prior to starting the resuscitation procedure, the pacing catheter was withdrawn to avoid injury during chest compression. After 15 min of untreated VF, CPR was started with the Thumper®. Chest compression was programmed to provide 100 compressions per min and synchronized to provide a compression/ventilation ratio of 30:2 with equal compression–relaxation intervals, i.e. a 50% duty cycle. The compression depth was adjusted to decrease the anterior–posterior diameter by 25%. Coincident with starting precordial compression, the animal was mechanically ventilated with a tidal volume of 15 ml/kg and FiO_2 of 1.0. After 2 min of chest compression, one dose of epinephrine (30 μg/kg) was injected into the right atrium. After another 3 min of chest compression, one 150-J biphasic electrical shock was delivered between the right infraclavicular electrode and the apical electrode with a Heartstart XL defibrillator (Philips Medical Systems, Andover, MA). If an organized cardiac rhythm with mean aortic pressure of more than 60 mm Hg persisted for an interval of 5 min or more, the animal was regarded as successfully resuscitated. If ROSC was not achieved, CPR was resumed for 1 min prior to the next defibrillation attempt. This sequence was repeated until the animal was either successfully resuscitated or pronounced dead after a total of 15 min of CPR. Ensuing doses of epinephrine were injected at the 7th and 12th min following initiation of CPR. Aortic blood samples for plasma norepinephrine measurements were collected in an EDTA tube at 1 min prior and 5 min after the start of CPR. Blood samples were immediately centrifuged at 4000 rpm for 10 min and plasma was separated from cellular blood components and stored at −20 °C until analysis. After successful resuscitation, the animals were monitored in an intensive care setting for an additional 4 h. The brain and core temperatures, ECG, aortic pressure, right atrial pressure, and pulmonary artery pressure were continuously monitored as previously described.[16–18] After 4 h observation, the animals were euthanized with an intravenous injection of 150 mg/kg pentobarbital. Autopsy was performed on all animals.

2.3. Administration of cooling

Prior to the onset of cardiac arrest, the core temperature of all the animals was maintained at 38 °C by using warm or cold water bags. Cooling was induced by using the RhinoChill™ (BeneChill Inc., San Diego, CA) nasal catheter system. The RhinoChill™ device sprays a liquid non-absorbed coolant, 6-chain perfluorocarbon (perfluorohexane – PFH) propelled by oxygen into the nasal cavity. The liquid is volatile and evaporates instantaneously, thereby removing heat from the nasal cavity. The cold is transmitted to the brain hematogenously (not predominantly hematogenous during no flow), through the submucosal nasal venous plexuses and by direct conduction. Body cooling occurs later.[15] The intranasal catheters were positioned in the animal's nostrils, and the RhinoChill™ coolant was delivered at 0.8 ml/kg/min with oxygen at 1 l/kg/min. The cooling was initiated at the start of precordial compression and stopped once core temperature reached 34 °C or at 4 h, whichever occurred first. Within the 4 h, cooling was stopped once core temperature reached 34 °C and was restarted if core temperature increased above 34.5 °C. The temperature of the control group was not altered following induction of VF.

2.4. Statistical analyses

Continuous variables were presented as mean ± S.D., and student *t*-test was used to check the difference between groups. The Fisher's exact test was used for the comparison of the categorical

Table 1
Baseline measurements of the two groups.

	Control ($N=8$)	Cooled ($N=8$)	p
Weight (kg)	40.3 ± 2.5	40.9 ± 1.7	0.58
Arterial pH[a]	7.51 ± 0.06	7.53 ± 0.03	0.44
Arterial PO_2[a] (mm Hg)	93.4 ± 11.5	97.9 ± 9.8	0.68
Brain temperature (°C)	37.7 ± 0.18	37.8 ± 0.12	0.09
Core temperature (°C)	38.0 ± 0.01	38.0 ± 0.03	0.37
Preparation time (min)	142.3 ± 25.2	152.4 ± 21.5	0.40
Pentobarbital dosage (mg/kg)	40.0 ± 3.7	42.0 ± 4.3	0.33
Mean arterial blood pressure (mm Hg)	127.1 ± 16.7	128.9 ± 11.6	0.81

[a] Corrected for coincident blood temperature.

variables. A value of $p < 0.05$ was considered significant. Analyses were carried out using SPSS V.11.0 software (Chicago, IL).

3. Results

There were no significant differences in baseline measurements between the two groups, including brain and core temperatures (Table 1).

At 15 min of VF, immediately prior to the initiation of cooling, brain temperature was increased from baseline value by 0.2 °C in the hypothermic group (38.0 °C) and by 0.2 °C in the control group (37.9 °C). Similarly, core temperature was increased by 0.3 °C in the hypothermic group (38.3 °C) and by 0.2 °C in the control group (38.2 °C).

ROSC was achieved within min of initiation of cooling (7.3 ± 3.4 min) in the hypothermic group. At that time point, brain temperature was below baseline at 37.7 ± 0.3 °C in the hypothermic group (−0.1 ± 0.3 °C of baseline), but was 38.0 ± 0.4 °C in the control group (+0.3 ± 0.3 °C of baseline; $p = 0.01$). Pulmonary artery temperatures, on the other hand, were significantly above baseline in both groups but no different between groups (+0.3 ± 0.2 °C in the hypothermic group and +0.5 ± 0.2 °C in the control group; $p = 0.11$; Fig. 2).

ROSC was achieved in 7 of 8 of the hypothermic animals but only 2 of 8 in control animals (87.5% vs. 25%, $p = 0.04$). There was no significant difference in the number of shocks needed (7.0 ± 3.8 vs. 6.9 ± 2.0, $p = 0.94$) and the success rate of initial shocks (50% vs.12.5%, $p = 0.12$). However, the hypothermic group had a higher successful rate for overall defibrillation than the control group (58% vs. 10%, $p < 0.01$). The duration of CPR was also lower in the hypothermic group (7.3 ± 3.4 min vs. 12.9 ± 4.0 min, $p = 0.01$). Baseline CPP at the end of the first min of CPR was no different between the two groups (hypothermic: 15.9 ± 5.6 mm Hg vs. control: 11.9 ± 9.6 mm Hg, $p = 0.33$). However, CPP prior to initial defibrillation was significantly higher in the hypothermic group (cooled: 25.6 ± 7.0 mm Hg vs. control: 16.4 ± 3.7 mm Hg, $p = 0.01$) (Fig. 1). All animals achieving ROSC survived to 4 h.

Plasma norepinephrine concentrations were similar in the two groups after 15 min of VF arrest (before cooling: 2.3 ± 4.3 ng/ml in the hypothermic group and 1.5 ± 1.5 ng/ml in the control group, $p = 0.65$). However, norepinephrine levels prior to the first shock were numerically lower in the hypothermic group, but the difference was statistically insignificant (119.5 ± 64.1 ng/ml in hypothermic group and 210.9 ± 179.1 ng/ml in the control group, $p = 0.20$).

4. Discussion

In the current study in the pig, we have shown that intra-nasal cooling, started at the initiation of CPR, dramatically improved the ROSC rate following 15 min of untreated VF. It also facilitated the resuscitation effort by reducing CPR duration. Improvement in ROSC rates following early induction of hypothermia has previously been reported.[13] However, in that study, systemic cooling was established before the induction of VF. In the current study, cooling was purposefully started at the same time as CPR to simulate an actual clinical situation.

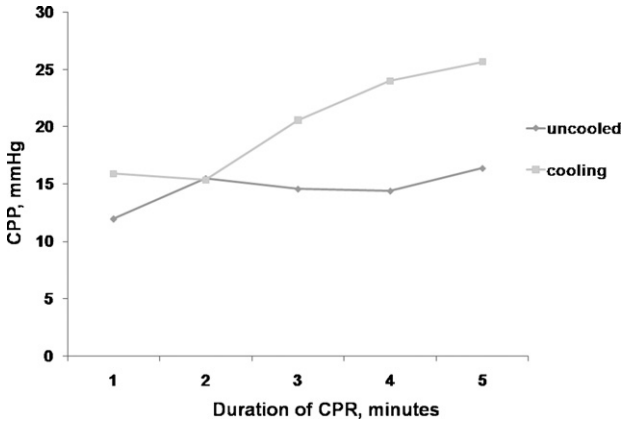

Fig. 1. Coronary perfusion pressure (CPP) during CPR.

The mechanism by which selective brain cooling improves the resuscitative effort and ROSC is still unclear. ROSC occurred, on average, 7 min after CPR was initiated in the hypothermic group, too short a time to invoke any of the cellular metabolic changes held responsible for the myocardial protective effect. Mechanical or electrical effects may have been responsible. It is conceivable that targeted cooling of the underside of the brain using nasopharyngeal cooling alters the firing rates of efferent autonomic nerves in the cervical chain. Inhibition of sympathetic firing during systemic hypothermia has previously been reported. In a study involving multifibre recordings of splenic, renal and adrenal sympathetic nerve activity during colonic cooling in rats, Helwig et al. found progressive reduction of sympathetic nerve discharge as temperature was reduced from 38 °C to 31 °C. Severe hypothermia during cardiopulmonary bypass and circulatory arrest has also been documented to decrease sympathetic nerve activity.[19] Conversely, increased cardiac sympathetic activity is associated with generation of ventricular tachyarrhythmias.[20,21] Lindner et al. demonstrated that plasma endogenous noradrenaline was lower during CPR in patients in whom resuscitation was successful than in those in whom it failed.[22] In this study, plasma norepinephrine concentrations did not differ significantly, the reduced efferent sympathetic discharge mechanism may not apply to our findings. Blecic et al. demonstrated that the administration of high doses of atropine together with epinephrine enhances the recovery from electromechanical dissociation and results in a better cardiac func-

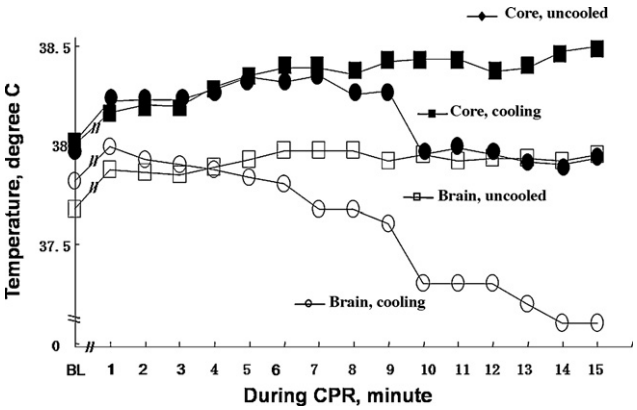

Fig. 2. Temperatures during precordial compression.

tion during recovery.[23] The vagal nerve activity reduction is another possible mechanism because the cooling also influences the vagal nerve function. However, this was not measured in this study.

This is the first report of an improved ROSC rate with selective brain cooling, without any direct myocardial cooling. Core temperature, as measured at the pulmonary artery, was 0.3 °C above baseline in the hypothermic group at the time ROSC was achieved. Thus, myocardial protection is achieved by cooling the brain rather than by direct myocardial cooling. Up to now, the beneficial effect of hypothermia on the myocardium has been attributed to changes in mechanical or cellular properties of the myocardium, reduced energy requirements, metabolic rate and cardiac output.[15]

The amount and duration of brain cooling required for enhancing ROSC may be different than that required for neuroprotection following cardiac arrest. Target temperature for neuroprotection has been shown to be 33–34 °C in many animal studies. The duration of hypothermia though, has been shown to be inversely proportional to the time of initiation following ischemic injury. Brief durations of hypothermia are neuroprotective if it is initiated prior to or including the time of ROSC,[24] but longer durations of hypothermia are required when cooling begins after ROSC.[8,9,12] Neither the amount nor duration of brain cooling required for enhancing ROSC has been determined. In this study, brain temperature was only 0.1 °C below the baseline value at ROSC, which occurred at 7 min of cooling. Furthermore, brain temperature in the control group was 0.3 °C above baseline, a difference of only 0.4 °C between the two groups. Improvement in ROSC rates may have occurred by preventing brain hyperthermia rather than induction of any significant hypothermia. We now need to confirm these findings and extend them to determine if much more significant cooling was present in the deeper regions of the brain, such as the inferior frontal lobe, hypothalamo-pituitary regions and brain stem, all of which are closer to the source of cooling in this method.

In this study, unlike our previous study[15] or the study of Boddicker et al.[13] coronary perfusion pressures were higher in the hypothermic animals just prior to the first defibrillation attempt. Threshold levels of CPP are known to be major determinants of successful resuscitation.[25,26] However, the increased CPP is unlikely to be attributable to sympathetic inhibition. Ganglionic blockade, for example, has been shown to decrease coronary blood flow[27] and presumably, CPP. Thus the reason for the increase in CPP and for the increased ROSC rates, remains unclear.

Several reports now suggest that very early cooling eases resuscitation and improves ROSC rates.[28] Current technology, however, allows only for induction of systemic hypothermia after resuscitation. Kim et al. and Klieqel et al. rapidly infused 2 L 4 °C normal saline within 6 h after admission to the hospital.[7,29] Uray et al. used cooling pads as early as 12 min after ROSC in an out-of-hospital setting to induce hypothermia.[30] However, surface cooling methods cannot be utilized during CPR because they are cumbersome and cooling rates are too slow and will likely have very little cooling effect on the brain within the relatively short resuscitation period. Intravenous cold saline infusions are a step in the right direction but may not provide enough cooling in the regions of the brain responsible for the beneficial effect during no-flow and low-flow states. Intra-nasal cooling may be an improvement both in speed of cooling and ease of administration.

There are several limitations to our study. First, we studied only a model of VF arrest. We now need to study the effect of intranasal cooling on PEA and asystole models if the method is to be used in non-VF arrest as well as VF. Second, it is difficult to blind the investigators in this study since touching the animals during the experiments allowed the investigators to differentiate between the hypothermic and control groups. Third, there was a small difference in temperature between the two groups, thus the improvement in ROSC rates may have occurred by preventing brain hyperthermia rather than induction of any significant hypothermia. The long-term neurologic outcomes of the animals were not compared in this study because of the very low ROSC in the control group. A further study using different cooling rates should be performed.

5. Conclusion

We have shown that intra-nasal cooling initiated at the start of CPR facilitates resuscitation and improves ROSC rates in animal models of VF arrest. Whether the beneficial effect also applies to non-VF arrest in animal models and whether these findings can be reproduced in humans needs to be determined in our further studies.

Conflicts of interest

Denise Barbut, MD is an employee of Benechill, Inc., San Diego, CA. The authors resident at the Weil Institute of Critical Care Medicine, Rancho Mirage, CA, USA, have not, nor will receive any individual benefits other than academic recognition.

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