

A comparison between head cooling begun during cardiopulmonary resuscitation and surface cooling after resuscitation in a pig model of cardiac arrest

Jun Guan, MD; Denise Barbut, MD; Hao Wang, MD; Yongqin Li, PhD; Min-Shan Tsai, MD; Shijie Sun, MD, FCCM; Becky Inderbitzen, MSEE; Max Harry Weil, MD, PhD, DSc (Hon), FCCM; Wanchun Tang, MD, FCCM

Objective: Employing transnasal head-cooling in a pig model of prolonged ventricular fibrillation, we compared the effects of 4 hrs of head-cooling started during cardiopulmonary resuscitation with those of 8 hrs of surface-cooling started at 2 hrs after resuscitation on 96-hr survival and neurologic outcomes.

Design: Prospective controlled animal study.

Setting: University-affiliated research laboratory.

Subjects: Domestic pigs.

Interventions: Twenty-four male pigs were subjected to 10 min of untreated ventricular fibrillation followed by 5 min of cardiopulmonary resuscitation. In the head-cooling group, hypothermia was started with cardiopulmonary resuscitation and continued for 4 hrs after resuscitation. In the surface-cooling group, systemic hypothermia with a cooling blanket was started, in accord with current clinical practices, at 2 hrs after resuscitation and continued for 8 hrs. Methods in the control animal studies were identical except for temperature interventions.

Measurements and Main Results: All animals were resuscitated except for one animal in each of the surface-cooling and control groups. After 5 min of cardiopulmonary resuscitation, jugular vein temperature was significantly decreased in the head-cooled animals. However, there were no differences in pulmonary artery temperatures among the three groups at that time. Nevertheless, both head-cooled and surface-cooled animals had an improved 96-hr survival after resuscitation. Significantly better neurologic outcomes were observed in early head-cooled animals in the first 3 days after resuscitation.

Conclusion: Early head-cooling during cardiopulmonary resuscitation continuing for 4 hrs after resuscitation produced favorable survival and neurologic outcomes in comparison with delayed surface-cooling of 8 hrs duration. (Crit Care Med 2008; 36: [Suppl.]:S428–S433)

KEY WORDS: therapeutic hypothermia; selective brain cooling; cardiac arrest; cardiopulmonary resuscitation; neurologic deficits

Although therapeutic hypothermia has been recommended by current international guidelines (1, 2) for comatose survivors of cardiac arrest due to its substantial beneficial impact on survival and

neurologic outcomes in clinical settings, the optimal target temperature, timing, and duration of hypothermia have not been defined. The guidelines recommended to cool the unconscious patients with return of spontaneous circulation (ROSC) to between 32°C and 34°C for 12 to 24 hrs (1, 2). However, this recommendation of duration was established based mainly on the proven outcomes of two successful randomized clinical trials (3, 4) and ease of implementation given that most comatose survivors are routinely sedated and ventilated over this period (1). No sufficient data had been shown to justify that 12 to 24 hrs of hypothermia is optimal for comatose patients after cardiac arrest (1). Interestingly, in the European study (3), the median interval between ROSC and initiation of cooling was 105 mins and the median duration of maintaining hypothermia was 24 hrs with an interquartile range of 12 to 29 hrs. In an Australian study (4), the initiation of cooling was started in the field and the median dura-

tion of hypothermia therapy was only 12 hrs with an interquartile range of 4 to 16 hrs. Both of these studies demonstrated significantly better survival and neurologic outcomes in hypothermia patients. Therefore, we may speculate that earlier initiation of therapeutic hypothermia and shorter duration of hypothermia would result in better outcomes.

Recent animal studies may support this speculation. Carroll et al. (5) investigated the neuronal protection of hypothermia in a gerbil model of global ischemia. They found that: 1) hypothermia during ischemia protects the brain from damage; 2) hypothermia initiated immediately after reperfusion must have a duration of 2 hrs or more to be effective; and 3) hypothermia initiated within 1 hr of reperfusion must have a duration of 6 hrs to be effective. Another study in a rat model of asphyxial cardiac arrest, Jia et al. (6) demonstrated that initiation of therapeutic hypothermia immediately after resuscitation with a 6-hr duration of hypothermia led to better functional outcomes com-

From the Weil Institute of Critical Care Medicine (JG, HW, YL, M-ST, SS, MHW, WT), Rancho Mirage, CA; The Keck School of Medicine of the University of Southern California (SS, MHW, WT), Los Angeles, CA; Benechill Systems (DB, BI), San Diego, CA; and Changzheng Hospital of the Second Military Medical University (JG), Shanghai, China.

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For information regarding this article, E-mail: drsheart@aol.com

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pared with conventional hypothermia initiated 1 hr after resuscitation with 12 hrs of hypothermia. Histopathologic assessment and quantitative electroencephalography analysis further verified this outcome. The above-mentioned studies suggested that early initiation of cooling might be more critical than duration of the treatment.

Furthermore, considering the cost, labor, and potential complications (3, 4, 7) related to a long interval of maintenance of hypothermia, this speculation might be of clinical significance. In the future, the duration of therapeutic hypothermia may be adjusted, based on the time of cardiac arrest and timing of initiation of the hypothermia rather than a fixed duration.

Therefore, from the present study on a pig model of prolonged cardiac arrest, we hypothesized that early head-cooling during cardiopulmonary resuscitation (CPR), continued for 4 hrs after resuscitation, produced outcomes comparable with that of delayed surface-cooling of 8 hrs duration.

METHODS

This study was approved by the Animal Use and Care Committee of the Weil Institute of Critical Care Medicine. 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 0-309-05337-3, revised 1996). The Weil Institute's laboratories are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Animal Preparation. Male Yorkshire-X domestic pigs (*Sus scrofa*) weighing 42 ± 3 kg were used in this study. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and completed by ear vein injection of sodium pentobarbital (30 mg/kg). A cuffed endotracheal tube was advanced into the trachea. Animals were mechanically ventilated with a volume-controlled ventilator (MA-1, Puritan-Bennett, Carlsbad, CA) with a tidal volume of 15 mL/kg, and F_{IO_2} of 0.21. End-tidal CO_2 was monitored with an infrared capnometer (01R-7101A, Nihon Kohden Corp, Tokyo, Japan). Respiratory frequency was adjusted to maintain $P_{et}CO_2$ between 35 and 40 mm Hg. For the measurement of aortic pressure, a fluid-filled catheter was advanced from the right femoral artery into the thoracic aorta. For the measurements of right atrial pressure, pulmonary arterial pressure, and

pulmonary artery temperature (PAT) as core body temperature, a 7F, thermodilution-tipped catheter was advanced from the right femoral vein and flow-directed into the pulmonary artery. For inducing ventricular fibrillation (VF), a 5F pacing catheter (EP Technologies, Inc.) was advanced from the right jugular vein into the right ventricle. The position of catheters was confirmed by characteristic pressure morphology and roentgenogram. The pacing catheter was removed after onset of VF. For measurements of retrograde jugular vein temperature (JVT), which was previously reported as an indicator of brain temperature (8, 9), another 5F catheter was inserted into the same internal jugular vein and passed in a retrograde direction as far as possible, typically 5 to 7 cm in depth.

The RhinoChill device (Benecill Inc., San Diego, CA) was used for inducing transnasal head-cooling. This device sprayed highly evaporative perfluorocarbon to the target area through a set of tubes, which were placed into nasal cavity and positioned into the nasopharynx for this study. During evaporation, the coolant absorbed a huge amount of heat, and therefore, cooled the nasopharynx.

surface-cooling was induced by a commercial water-blanket hypothermia system (Blanketrol II Hyper-Hypothermia System, Cincinnati SubZero, Cincinnati, OH).

Experimental Procedures. Fifteen minutes before inducing cardiac arrest, PAT was adjusted to $38^\circ C$ by using a heating lamp, warm packs or ice packs, to obtain baseline measurements. Twenty-four animals were assigned to: 1) a head-cooling group, 2) a surface-cooling group, and 3) a control group, with eight in each group. In the transnasal head-cooling group, the tubing set of the RhinoChill was placed into the nasopharynx to deliver coolant for inducing head-cooling. Cardiac arrest due to VF was induced by a 1 mA alternating current through a 5F pacing catheter (EP Technologies, Inc.) delivered to the right ventricular endocardium. Mechanical ventilation was discontinued after onset of VF. Before the start of the resuscitation procedure, the pacing catheter was withdrawn to avoid injury to the myocardium during chest compression. At the end of 10 mins of untreated VF, CPR was started with chest compression using a pneumatic piston-driven chest compressor (Thumper 1000, Michigan Instruments, Grand Rapids, MI). Animals were mechanically ventilated with 100% oxygen. Chest compression was programmed to provide 100 compressions per minute 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 optimize the real-time coronary perfusion pressure. After 2 mins of CPR, the first bolus of epinephrine at a dose of 30 $\mu g/kg$ was given via the right atrial catheter. After 5 mins of CPR, the first defibrillation was attempted with a single 150-J biphasic electrical shock delivered between the conventional

right infraclavicular electrode and the apical electrode using a Heartstart XL defibrillator (Philips Medical Systems, Andover, MA). If an organized cardiac rhythm with a mean aortic pressure (MAP) of more than 60 mm Hg of spontaneous circulation was not restored and VF still existed, mechanical chest compression and mechanical ventilation were resumed for 1 min before the next defibrillation attempt. Additional doses of epinephrine were given at 7, 10, and 12 mins after the start of CPR until ROSC. Once an organized rhythm with a MAP of more than 60 mm Hg and ROSC, the following recurrent VF was treated with successive 150-J defibrillations without delay until ROSC. During any CPR period, pulseless electrical activity was treated with continuous chest compression and ventilation at a ratio of 30:2. An organized cardiac rhythm with a MAP of more than 60 mm Hg which persisted for an interval of 10 mins or more fulfilled our criteria of successful resuscitation; otherwise, resuscitation procedures would be continued for a maximum of another 10 mins. For the head-cooling group, the RhinoChill device was started at the beginning of CPR and continued until PAT achieved $34^\circ C$. The cooling procedure was resumed if core body temperature was above $34.5^\circ C$. The cooling procedure covered the 4-hr postresuscitation period. In the surface-cooling group, blanket cooling was started at 2 hrs after resuscitation and continued until PAT achieved $34^\circ C$. The cooling procedure was resumed if PAT was above $34.5^\circ C$. The cooling procedure continued until 10 hrs after resuscitation. In control animals, the preparation and resuscitation procedures were identical except that no cooling intervention was implemented.

After resuscitation, the head-cooling animals and control animals were monitored in an intensive care setting for an additional 4 hrs and hemodynamics were obtained hourly during the observation period. JVT and PAT were obtained every minute until 30 mins after resuscitation, then every 10 mins throughout the experiment. After the panel of 4-hr postresuscitation measurements and cooling procedures had been completed, intravascular catheters were removed and wounds were surgically sutured. The animals were then passively rewarmed and returned to their cages and observed until 96 hrs after resuscitation. The surface-cooling animals were monitored and treated in the same manner until 10 hrs after resuscitation. Neurologic Deficit Scores (NDS) developed by Berg et al. (10) were obtained daily during the 96-hr postresuscitation observational interval. The animals were then killed by injection of 150 mg/kg intravenous pentobarbital. At the end of the experiment, autopsy was routinely performed on each animal for documentation of significant injuries to the bony thorax and thoracic and abdominal viscera.

Measurements. The primary observations of this study were the 96-hr postresuscitation survival, and postresuscitation NDS. The sec-

ondary observation was the ejection fraction as an indicator of myocardial function.

The NDS was used for evaluating neurologic injury at 24-hr intervals for a total of 96 hrs. Briefly, NDS consists of level of consciousness, motor and sensory function, respiratory pattern, and behavior. The neurologic deficits were scored from 0 (no observed neurologic deficit) to 400 (death or brain death). Two investigators measured the NDS independently and reached agreement.

Other measurements were recorded to test for population bias and to assist in consistent performance of the resuscitation protocol. Measurements of the aortic and right atrial pressures allowed for estimation of coronary perfusion pressure. End-tidal CO₂ was measured continuously to provide as indication of appropriate ventilation and as a quantitative indicator of relative pulmonary blood flow during precordial compression.

Hemodynamic data, including aortic artery, right atrial, and pulmonary artery pressures, end-tidal PCO₂, and the lead II electrocardiogram were continuously measured and recorded on a personal computer-based data acquisition system, supported by Computer Data Acquisition System (CODAS, Cambridge, MA) as previously described (11). Ejection fraction was measured with the aid of HD11XE, Ultrasound System Specification, (Philips Medical System, Eindhoven, The Netherlands).

Arterial blood gases were measured with a blood gas analyzer (1306, Instrumentation Laboratory, Lexington, MA) adapted for porcine blood. Arterial blood lactate was measured with a lactic acid analyzer (23L, Yellow Springs Instruments, Yellow Springs, OH). These measurements were obtained 15 mins before cardiac arrest and at hourly intervals after resuscitation for a total of 4 hrs.

Analysis. Data with normal distribution were expressed as mean ± SEM. Nonnormal distributed data were expressed as median (first quartile, third quartile). Fisher's exact test was used to compare initial success of resuscitation and 96-hr survival between the groups.

Pearson's correlation test was performed to test the significance of the correlation between JVT and PAT in surface-cooling animals and control animals. Analysis of variance was performed to identify the differences in body weight, MAP, heart rate, ejection fraction, PAO₂, base excess, and lactate among the three groups. Scheffe's test was used for further *post hoc* pairwise comparison between the groups. The Kruskal-Wallis test was performed to identify overall difference of NDS among the three groups. The Mann-Whitney test was further performed to identify the difference between groups. All the statistical analyses were performed with the use of SPSS 9.0 (SPSS Inc, Chicago, IL). For all statistical analyses, a probability value of ≤0.05 was considered significant.

Table 1. Baseline characteristics

	head-cooling (n = 8)	surface-cooling (n = 8)	Control (n = 8)	<i>p</i>
Body mass, kg	40.4 ± 0.3	41.0 ± 1.2	40.8 ± 0.7	0.864
Mean aortic pressure, mm Hg	116 ± 4	125 ± 4	123 ± 4	0.268
Heart rate, beat/min	132 ± 12	158 ± 13	148 ± 11	0.293
Ejection fraction, %	65.0 ± 0.9	63.2 ± 0.7	63.4 ± 0.9	0.268
Lactate, mg/L	1.3 ± 0.3	1.5 ± 0.2	0.9 ± 0.1	0.200
PAO ₂ , mm Hg	102.9 ± 3.5	101.1 ± 6.7	101.3 ± 5.5	0.968
Base excess, mEq/L	6.3 ± 0.8	8.2 ± 1.2	6.8 ± 1.1	0.429

Data are given as mean ± SEM.

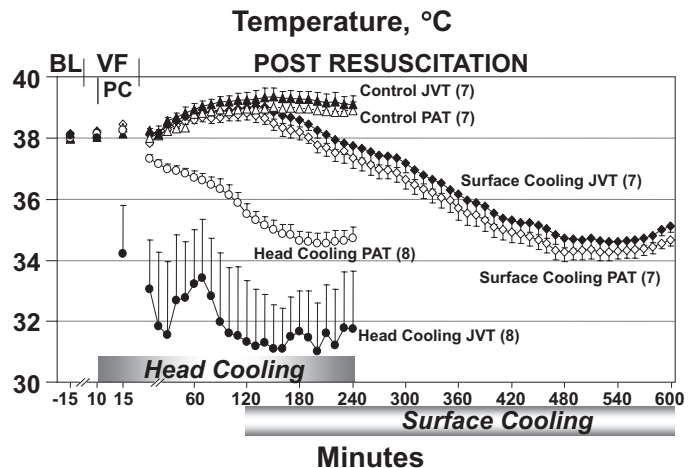


Figure 1. Temperature before, during, and after cardiopulmonary resuscitation. Solid legends represent retrograde jugular vein temperature (JVT), empty legends represent pulmonary artery temperature (PAT). In the head-cooling group, cooling was started at the start of precordial compression (PC). In the surface-cooling group, cooling was started at 2 hrs after resuscitation. Values are mean ± SEM. BL, baseline; VF, ventricular fibrillation.

RESULTS

Baseline and CPR Characters. There were no significant differences among the groups in baseline characteristics, including body weight, MAP, ejection fraction, heart rate, lactate, base excess, and arterial oxygen pressure ($p > .05$) (Table 1).

All animals were successfully resuscitated except for one each in the control group and the surface-cooling group ($p > .05$).

Temperature Change. There were no significant differences among groups at baseline and 10 mins after VF for both JVT and PATs (Fig. 1). After 5 mins of CPR, JVT was $38.3 \pm 0.1^\circ\text{C}$ in the surface-cooled animals and $38.1 \pm 0.1^\circ\text{C}$ in control animals, compared with $34.2 \pm 1.6^\circ\text{C}$ in the head-cooled animals ($p < .01$); there were no differences in PAT among the three groups at that time. After resuscitation, the body temperature was decreased gradually as well as JVT in the head-cooling group; the JVT-PAT gradient was 2.9°C to 5.5°C on average during

the heading-cooling interval. The JVTs were less than 0.5°C higher than the coincident PATs and highly correlated in the surface-cooling group ($r = .998, p < .01$) and control group ($r = .965, p < .01$) after resuscitation. The median time to reach 34.0°C of PAT after resuscitation was 475 mins in the surface-cooling group and 215 mins in the head-cooling group. The median time to reach 34.0°C of JVT after resuscitation was 530 mins in the surface-cooling group and 25 mins in the head-cooling group. The highest PAT temperature was $38.9^\circ\text{C} \pm 0.2^\circ\text{C}$ in the surface-cooling group and $39.3^\circ\text{C} \pm 0.2^\circ\text{C}$ in the control group. The highest JVT was $39.1^\circ\text{C} \pm 0.2^\circ\text{C}$ in the surface-cooling group and $39.5^\circ\text{C} \pm 0.3^\circ\text{C}$ in the control group.

Ninety-six Hours Survival. All eight animals in the head-cooling group (100%), six of seven animals (85.7%) in surface-cooling group, and two of seven animals (28.6%) in control group survived to 96 hrs after resuscitation ($p = .005$). Survival rate was significantly higher in the head-cooling group than that in the control

Table 2. Neurological deficit scores after resuscitation

Hours Post-ROSC	Head (8) ^{a,c}	Surface (7) ^{a,c}	Control (7) ^{a,c}	p ^b
24	60 (23, 70)	195 (185, 223)	400 (288, 400)	0.000
48	0 (0, 28)	95 (65, 100)	400 (215, 400)	0.005
72	0 (0, 0)	40 (20, 80)	400 (205, 400)	0.006
96	0 (0, 0)	0 (0, 40)	400 (205, 400)	0.008

^aNeurological Deficit Score (NDS), 400 = death or brain death, 0 = normal; ^bOverall effect (Kruskal-Wallis test); ^cNDS expressed as median (quartile1, quartile3).

ROSC, return of spontaneous circulation.

group ($p = .007$) but was not significantly different from that in the surface-cooling group ($p = .467$). Survival rate in the surface-cooling animals was significantly better than in the control animals ($p = .041$) at 24 hrs, but not significant ($p = .132$) at 96 hrs after resuscitation.

Neurologic Outcomes. Neurologic outcomes are illustrated in Table 2. Significantly better NDS were observed in the head-cooling group in comparison with control animals at all time points after resuscitation ($p < .01$) and with surface-cooled animals at 24 hrs ($p = .001$), 48 hrs ($p = .004$), and 72 hrs ($p = .013$) after resuscitation. There was no significant difference between the head-cooled and surface-cooled animals at 96 hrs after resuscitation ($p = .137$). Surface-cooled animals showed significantly better neurologic outcomes at 24 hrs after resuscitation ($p = .045$) and a strong trend toward better neurologic outcomes ($p = .056$) at 96 hrs after resuscitation.

DISCUSSION

This study on large animals demonstrated that early transnasal head-cooling started with CPR and continued for 4 hrs after resuscitation produced outcomes comparable with that of delayed surface-cooling of 8 hrs duration in a pig model of prolonged cardiac arrest.

Induction of therapeutic hypothermia after ROSC has already been demonstrated to be associated with improved survival and neurologic outcomes in various animal models of cardiac arrest (12–15). On the basis of two landmark randomized clinical studies (3, 4), 12 to 24 hrs of therapeutic hypothermia were recommended by the American Heart Association, the European Resuscitation Council, and the International Liaison Committee on Resuscitation for the unconscious patients with spontaneous circulation after cardiac arrest (1, 2). Practices from recently published clinical studies were in accordance with this recommendation (16,

17). Meanwhile, the guidelines (1) called for further research on the optimal initiation time, duration of therapy, and depth of hypothermia. Although impressive therapeutic benefit still could be shown in animal studies (5, 18–26) and clinical studies (3, 4, 16, 17) when cooling was delayed for several hours, most animal studies (5, 19, 21–24) unanimously established that earlier implementation of hypothermia during or after CPR would produce better functional outcomes. However, few studies have focused on the duration of hypothermia and specifically its relationship to the timing of initiation of hypothermia. When considering the cost, labor, and potential increasing risks of side effects of long-time maintenance of hypothermia (3, 4, 7, 16, 17), research for optimal duration is of clinical significance. Therefore, we tested the hypothesis in the present study that early head-cooling during CPR and for 4 hrs after resuscitation produced outcomes comparable with that of conventional surface-cooling of 8 hrs duration on a pig model of prolonged cardiac arrest.

Previous experiments (5) on a gerbil model of global ischemia demonstrated that protection against hippocampal CA1 cell loss by postischemic hypothermia is dependent on the delay of initiation and duration. Therefore, with the earlier initiation of hypothermia, the shorter duration of therapy is necessary for the effective protection of neuronal damage. Similarly, Jia et al. (6) demonstrated in an asphyxial cardiac arrest model that earlier (immediately after ROSC) but shorter (6 hrs) hypothermia delivery yielded better functional outcome compared with conventional hypothermia (i.e., 1 hr after ROSC and 12 hrs duration). To date, no single clinical study has focused on the optimal duration of hypothermia for unconscious patients after cardiac arrest. As opposed to the European study where the initiation of cooling

was 105 mins after ROSC with a duration of 12 to 29 hrs (3), the Australian study (4) used an initiation time of approximately 2 hrs earlier with only half of the cooling duration (12 vs. 24 hrs). In the present study, we demonstrated that intranasal head-cooling initiated with CPR and continued for 4 hrs after ROSC yielded a comparable 96-hr survival outcome and quicker recovery of neurologic deficit than conventional surface-cooling for twice the cooling duration (8 hrs). The myocardial function at 96 hrs after resuscitation, as indicated by ejection fraction, was significantly better in the early head-cooling group. The above-mentioned studies and our data suggested that earlier initiation of hypothermia might be crucial for the recovery of neurologic injury associated with cardiac arrest.

Two different, but closely related kinds of brain injury are associated with cardiac arrest and CPR (15, 27–31): ischemia and subsequent reperfusion. Briefly, within 4 to 5 mins of cardiac arrest, brain glucose and adenosine triphosphate stores are lost because of complete cerebral anoxia and ischemia (30–32). The consecutive dysfunction of neuronal membrane pumps and membrane depolarization lead to a number of cytotoxic events (27–31), including influx of calcium, lactate acidosis, glutamate release, generation and accumulation of free fatty acids, free radicals (33–35), and excitatory amino acids (20). These events are actually interactive, ongoing and in a cascade of burst, and finally lead to neuron necrosis or apoptosis (15, 27, 31). Inflammatory response also occurs in the reperfusion injury phase (20, 36–38), which was characterized by production of transcription factor nuclear factor- κ B, tumor necrosis factor, adhesion molecules, and leukocytes invasion. The post-ischemic inflammatory cascade would finally lead to a net increase in tissue injury. Furthermore, disturbance of cerebral blood flow adds to the extent of neuronal injury after cardiac arrest, which is characterized by increased vascular permeability and edema formation (21, 30, 32).

Large bodies of evidence have demonstrated the beneficial effect of hypothermia on the brain following ischemia and reperfusion injury. Because hypothermia is typically implemented after ROSC or during CPR in several recent studies (12, 19, 24, 39–41), the beneficial effect of hypothermia occurs in the reperfusion phase for cardiac arrest patients. Hypothermia had

been proved to suppress many of the chemical reactions associated with reperfusion injury (20, 27, 28, 30), as well as inflammatory reactions (15, 27, 30, 37, 38), and edema formation (15, 21). These chemical reactions include free radical production, excitatory amino acid release, and calcium influx. Most importantly, hypothermia seems to have the ability to affect multiple systems simultaneously, and this may be the reason for its efficacy in improving neurologic outcomes after cardiac arrest (30). Therefore, it is reasonable to conclude that the earlier the initiation of hypothermia during the reperfusion injury process, the less intense are the cascade reactions, and the less severe is the secondary injury.

The protective effect of surface-cooling seems to be weak in the present study. Compared with the control group, neurologic outcome and survival after resuscitation in the surface-cooling group were better numerically, but only statistically significant at 24 hrs after resuscitation. No difference was found in ejection fraction between the two groups. This may have resulted from the gradual rising of head temperature and body temperature as in control animals until 2 hrs after resuscitation. The highest head temperature was $39.1^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ in the surface-cooling group and $39.5^{\circ}\text{C} \pm 0.3^{\circ}\text{C}$ in the control group. Hyperthermia had been shown to be associated with worse neurologic outcomes in animal studies (42, 43) and human studies (44, 45). The small sample number in the present study may also decrease the power to detect the beneficial effect of delayed surface-cooling.

Intranasal head-cooling was selected as an early hypothermia method in the present study. One advantage of this method is that when the cooling power is focused on brain, the organ most vulnerable to ischemia-reperfusion injury, much time is saved in reaching the target temperature. In the present study, the JVT was rapidly decreased to 34.0°C within a median of 25 mins after resuscitation. This result is consistent with the study by Covaciu et al. (46), showing that a mean decrease of 2.8°C of cerebral temperature was achieved within 20 mins by an intranasal brain-cooling method in anesthetized pigs. Therefore, even if the target body temperature is not fully achieved, the quickly cooled brain would be protected by hypothermia at a very early stage after resuscitation. Furthermore, if less power is necessary, the de-

vice would be more portable and can be used more quickly in the field.

Another advantage is that when side effects of hypothermia are counterbalanced, selective brain cooling is safer. After resuscitation from cardiac arrest, cardiogenic shock or life-threatening arrhythmias are not uncommon (45). This hemodynamic instability may last for several hours and may exclude some of the cardiac arrest victims from early systemic hypothermia therapy based on current guidelines (45). Other complications, such as coagulopathy, sepsis, and hyperglycemia (3, 4, 16, 17, 45) may further preclude particular patients with high risks for these problems. Selective head-cooling with subsequent delayed systemic hypothermia, as shown in the present study, would create a safe window for the possible ultra-early delivery of hypothermia in out-of-hospital settings in the future, therefore maximize neuroprotection yet minimize systemic complications (47).

In the present study, we do not intend to define the precise optimal duration of hypothermia after cardiac arrest. The therapeutic hypothermia formula (depth and duration) should be individualized based on the timing of cardiac arrest, duration and pathophysiologic conditions. Objective monitoring of brain function should be used as a guide for hypothermia therapy, e.g., quantitative electroencephalography (6).

There were certain limitations to this study: 1) This was not a randomized animal study. Sixteen animals were randomized into a head-cooling group and a control group, another eight animals were assigned later to a surface-cooling group. There were no significant differences in major baseline physiologic variables among the three groups to suggest a lack of bias in triage. 2) The investigators who evaluated the NDS could not be blinded for the treatment groups due to obvious different settings and unavailability of other personnel. However, agreement between the two investigators in this study was satisfactory, similar to that reported by other investigators (48). 3) Retrograde JVT was used as an indicator of brain temperature as previously reported (8, 9). Although the tip of the temperature sensor was located at the base of skull, we recognize that it is not equal to the actual brain temperature due to its extracranial position. There were large standard deviations of JVTs in the head-cooled animals after initiation of intranasal head-cooling. The differences may have been partially due to the variability in the distance between

the temperature sensor and cooling tube set. However, this JVT can at least be taken as an indicator of regional temperature of the skull base.

CONCLUSION

We conclude that early intranasal head-cooling during CPR and for 4 hrs after resuscitation produced outcomes comparable with that of delayed surface-cooling of 8 hrs duration in a pig model of prolonged cardiac arrest.

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