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Rapid Induction of Cerebral Hypothermia Is Enhanced With Active Compression-Decompression Plus Inspiratory Impedance Threshold Device Cardiopulmonary Resusitation in a Porcine Model of Cardiac Arrest

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OBJECTIVES A rapid, ice-cold saline flush combined with active compression-decompression (ACD) plus an inspiratory impedance threshold device (ITD) cardiopulmonary resusitation (CPR) will cool brain tissue more effectively than with standard CPR (S-CPR) during cardiac arrest (CA).

BACKGROUND Early institution of hypothermia after CPR and return of spontaneous circulation improves survival and outcomes after CA in humans.

METHODS Ventricular fibrillation (VF) was induced for 8 min in anesthetized and tracheally intubated pigs. Pigs were randomized to receive either ACD + ITD CPR (n = 8) or S-CPR (n = 8). After 2 min of CPR, 30 ml/kg ice-cold saline (3°C) was infused over the next 3 min of CPR via femoral vein followed by up to three defibrillation attempts (150 J, biphasic). If VF persisted, epinephrine (40 μg/kg) and vasopressin (0.3 U/kg) were administered followed by three additional defibrillation attempts. Hemodynamic variables and temperatures were continuously recorded.

RESULTS All ACD + ITD CPR pigs (8 of 8) survived (defined as 15 min of return of spontaneous circulation [ROSC]) versus 3 of 8 pigs with S-CPR ($p < 0.05$). In survivors, brain temperature (°C) measured at 2-cm depth in brain cortex 1 min after ROSC decreased from 37.6 ± 0.2 to 35.8 ± 0.3 in ACD + ITD CPR versus 37.8 ± 0.2 to 37.3 ± 0.3 in S-CPR ($p < 0.005$). Immediately before defibrillation: 1) right atrial systolic/diastolic pressures (mm Hg) were lower (85 ± 19, 4 ± 1) in ACD + ITD CPR than S-CPR pigs (141 ± 12, 8 ± 3, $p < 0.01$); and 2) coronary perfusion pressures (mm Hg) were higher in ACD + ITD CPR (28.3 ± 2) than S-CPR pigs (17.4 ± 3, $p < 0.01$).

CONCLUSIONS A rapid ice-cold saline infusion combined with ACD + ITD CPR during cardiac arrest induces cerebral hypothermia more rapidly immediately after ROSC than with S-CPR. (J Am Coll Cardiol 2006;47:835–41) © 2006 by the American College of Cardiology Foundation

Recent clinical trials of induced hypothermia have shown improved outcomes in comatose survivors of out-of-hospital cardiac arrest (CA) (1–3). Animal studies suggest that anoxic brain injury may be reduced if hypothermia is induced during or immediately after CA (4–8). Myocyte cell culture studies demonstrate that cooling delay after ischemia results in rapid cell death (9). Thus, techniques that rapidly establish hypothermia during CA with chest compressions may be clinically important. One practical method of achieving hypothermia in the setting of CA is rapid infusion of cold (4°C) intravenous (IV) fluid to induce mild hypothermia in comatose survivors of out-of-hospital CA (10).

While cooling during cardiopulmonary resuscitation (CPR) may be advantageous, standard American Heart Association (AHA) recommended chest compressions only produce 10% to 25% of normal blood flow to the heart and brain during CPR (11–14). We, therefore, hypothesized that techniques that could increase vital organ perfusion during CPR would facilitate rapid cooling during CA. In this regard, use of an inspiratory impedance threshold device (ITD) combined with an active compression-decompression (ACD) device increases cardiopulmonary and cerebral blood flow to near normal values (Fig. 1). Use of these devices significantly increases survival rates after CPR (15–19). Building on these studies, we tested the hypothesis that the efficacy of a rapid, ice-cold saline infusion combined with ACD + ITD CPR would cool brain tissue more effectively than with S-CPR during CA.

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Abbreviations and Acronyms

ACD = active compression-decompression
AHA = American Heart Association
CA = cardiac arrest
CPR = cardiopulmonary resuscitation
ITD = impedance threshold device
IV = intravenous
ROSC = return of spontaneous circulation
S-CPR = standard cardiopulmonary resuscitation
VF = ventricular fibrillation

METHODS

With committee on animal experimentation approval, all animals were managed in accordance with the guidelines of the American Physiological Society, University of Minnesota, and the AHA.

Preparatory phase. Sixteen healthy, 12- to 16-week-old female domestic farm pigs weighing 16 to 33 kg were anesthetized with 500 to 700 mg intramuscular ketamine (Ketaset, Fort Dodge Animal Health, Fort Dodge, Iowa) and propofol (PropoFlo, Abbott Laboratories, North Chicago, Illinois) IV (2 to 3 mg/kg). After intubation with a 7.5-mm cuffed endotracheal tube (Mallinckrodt Critical Care, Glens Falls, New York), anesthesia was maintained by propofol infusion (125 μg/kg/min). Animals were mechanically ventilated (Model 607, Harvard Apparatus Co., Dover, Massachusetts) with tidal volumes of 20 ml/kg, and respiratory frequency was adjusted from 10 to 12 breaths/min to maintain an end-tidal carbon dioxide partial pressure of 35 to 40 mm Hg; inspiratory oxygen concentration was titrated to maintain oxygen saturations of >96% during preparation.

High-fidelity micromanometer-tipped catheter (Millar Instruments Inc., Houston, Texas) pressure transducers and a fiberoptic transducer-tipped pressure-temperature catheter (Camino, Integra NeuroSciences, Plainsboro, New Jersey) were inserted via burr holes approximately 2 cm into the parietal lobes for digital acquisition and recording (Superscope II, v1.295, GW Instruments, Somerville, Massachusetts) of intracranial pressure and temperature.

Micromanometer-tipped catheters (Mikro-Tip Transducer, Millar Instruments Inc.) were placed to continuously record central thoracic aortic and superior vena cava blood pressures. A 10-F central venous catheter was placed in the right femoral vein for infusion of ice-cold (3°C) normal saline, with a heparin bolus (100 U/kg) given once all catheters were in place. Thermistor probes recorded central abdominal aorta arterial, esophageal (Mon-a-therm, Mallinkrodt Inc., St. Louis, Missouri), nasopharyngeal, and rectal (Type K thermocouple Probe, Dual channel Termometer, Control Company, Frienfwood, Texas) temperatures (°C). Intratracheal pressures were continuously measured using a micromanometer-tipped catheter positioned 2-cm below the distal tip of the endotracheal tube.

Experimental protocol. After surgical preparation and stabilization, ventricular fibrillation (VF) was induced by 50 Hz, 7.5 V AC right ventricle electrical current via pacing wire, and the ventilator was disconnected from the endotracheal tube. After 8 min of untreated VF, animals were randomized to receive either closed-chest standard CPR with a sham ITD (S-CPR) or closed-chest ACD CPR with a functional ITD (Advanced Circulatory Systems, Inc., Eden Prairie, Minnesota) with a cracking pressure set to −10 cm H_2O (ACD + ITD CPR). All CPR was performed continuously with a pneumatically driven automatic piston device (prototype ACD Controller, AMBU International, Glen Burnie, Maryland) positioned over the lower third of the sternum, as previously described (14–16). The compression rate was 100/min with a 50% duty cycle, and a depth of 25% of the anterior-posterior diameter of the chest wall. With ACD + ITD CPR, active decompression upward suction was approximately 25 lbs. For S-CPR, there was no active decompression, and the chest recoiled passively and freely, without resistance from the weight of the compression piston. During performance of either CPR, animals received 450-ml tidal volume ventilation with 100% O_2, at a compression-to-ventilation ratio of 15:2. Each breath was initiated at the start of the chest wall decompression phase.

After 2 min of CPR, 30 ml/kg of ice-cold (3°C) saline was infused over 3 min via the right femoral vein during CPR. The saline infusate temperature was maintained by ice slurry and circulating ice-cold water infusion pump tubing immersion (Flo-Gard 6201; Baxter Healthcare, Hooksett, New Hampshire). At the end of the 3-min infusion and after a total of 5 min of CPR, defibrillation was attempted (ZOLL, Chelmsford, Massachusetts). Biphasic shocks of 150 J were delivered up to a maximum of three times. If VF or a non-VF, non-perfusing rhythm persisted, CPR was

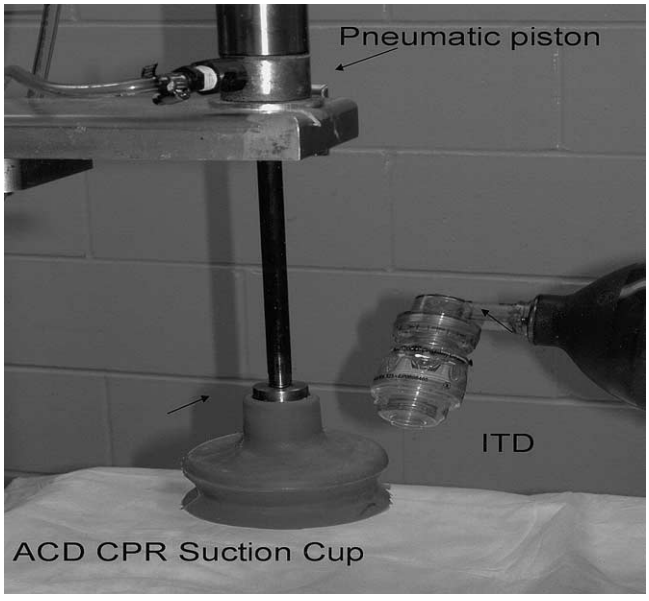

Figure 1. Active compression-decompression (ACD) cardiopulmonary resuscitation (CPR) with impedance threshold device (ITD).

continued for another 2 min, and epinephrine was given at a dose of 40 μg/kg combined with vasopressin at a dose of 0.3 U/kg. In the case of VF rhythm, this was followed by the delivery of up to three more shocks (150 J). If VF or a non-VF, non-perfusing rhythm persisted, further resuscitation efforts were terminated. When resuscitation was successful (return of spontaneous circulation [ROSC]), animals were ventilated with positive pressure at a rate of 12 breaths/min and tidal volume of 500 ml. No further interventions were performed after restoration of spontaneous circulation. Hemodynamic parameters and temperatures were monitored during ROSC for 15 min. At the end of the protocol, the animals were euthanized with IV boluses of propofol and potassium chloride. The timeline of the experimental protocol is shown in Figure 2.

Measurements. Pressure tracings obtained from the high-fidelity micromanometer catheters were continuously monitored with a data acquisition (Superscope II v1.295, GW Instruments) and computerized recording system (Apple Macintosh). Coronary perfusion pressure calculated during diastole (relaxation) was defined as the arteriovenous pressure difference (time-coincident difference between aortic and right atrial pressure). Cerebral perfusion pressure calculated during diastole (relaxation) was defined as the arteriovenous pressure difference (time-coincident difference between aortic and intracranial pressure).

End-tidal carbon dioxide and arterial oxygen saturation was recorded with a CO2SMO Plus (Novametrix Medical Systems, Wallingford, Connecticut). Temperature-corrected arterial blood gases were analyzed (IL 1301, Instrumentation Laboratory, Lexington, Massachusetts) at multiple times during the experimental protocol. Temperatures were measured at 1-min intervals from the start of the experiment until 5 min after ROSC and then at 5-min intervals thereafter.

Statistical analysis. The primary outcome variable was the intracranial temperature at 2-cm depth in the brain cortex during ROSC. Other outcome variables analyzed included gradient between arterial and cranial temperatures during fluid infusion, change in coronary and cerebral perfusion pressures with fluid infusion, and survival to ROSC. All values are expressed as mean ± SEM. The sample size was calculated a priori on the basis of expected difference in rate of intracranial cooling between the two groups. Baseline characteristics were compared using the *t* test for normally distributed continuous variables, and the Wilcoxon rank sum test for continuous variables that were not normally distributed. Lilliefors test of normality was used to determine if continuous variables were normally distributed or not. Survival outcomes were analyzed with Fisher exact test. Results were considered to be statistically significant if $p < 0.05$.

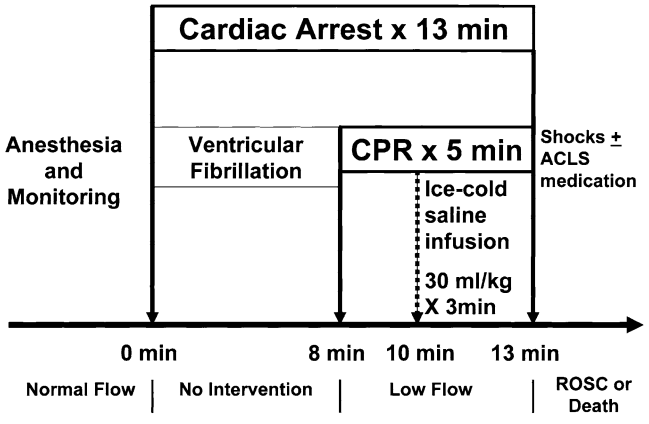

Figure 2. Timeline of experimental protocol. ACLS = advanced cardiac life support; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation.

Table 1. Baseline (Pre-Arrest) Characteristics*

	ACD + ITD CPR (n = 8)	S-CPR (n = 8)
Weight, kg	25.5 ± 2	25.3 ± 2
Hematocrit, %	31.4 ± 2	31.3 ± 1
Total propofol dose, mg	463 ± 34	349 ± 44
Aortic systolic pressure, mm Hg	101 ± 5	97.4 ± 6
Aortic diastolic pressure, mm Hg	86.7 ± 6	81.9 ± 7
Right atrial systolic pressure, mm Hg	1.3 ± 1	3.4 ± 1
Right atrial diastolic pressure, mm Hg	−0.5 ± 1	0.3 ± 1
Coronary perfusion pressure, mm Hg	92.5 ± 7	88.7 ± 3
Intracranial pressure, mm Hg	19 ± 1	17.6 ± 2
Cerebral perfusion pressure, mm Hg	77.5 ± 4	74.9 ± 6
Brain temperature, °C	37.6 ± 0.2	37.8 ± 0.3

*All values are expressed as mean ± SEM.
ACD + ITD CPR = active compression-decompression cardiopulmonary resuscitation with impedance threshold device; S-CPR = standard cardiopulmonary resuscitation with sham ACD and ITD devices.

RESULTS

Eight pigs were randomized to receive S-CPR, and eight received ACD + ITD CPR. Both groups were comparable by *t* test for pre-arrest hemodynamic and temperature variables (Table 1).

After 8 min of VF, intracranial temperatures (37.6 ± 0.2°C in the ACD + ITD CPR group vs. 37.8 ± 0.2°C in the S-CPR group, $p = 0.5$) and intracranial pressures (23.1 ± 1 mm Hg in the ACD + ITD CPR group vs. 22.4 ± 1 mm Hg in the S-CPR group, $p = 0.7$) were similar. During the initial 2 min of CPR before ice-cold saline infusion, the ACD + ITD CPR group tended to have higher coronary and cerebral perfusion pressures than the S-CPR group (Table 2). During ice-cold saline infusion, the right atrial diastolic pressures were higher in S-CPR (8 ± 3 mm Hg) than ACD + ITD CPR (4 ± 1 mm Hg, $p < 0.05$) when compared with pre-infusion values. The cold saline infusion resulted in a corresponding decrease in coronary perfusion pressures in both groups, significantly in the S-CPR group (Table 2). The ACD + ITD CPR group had higher coronary perfusion pressures ($p < 0.05$) and cerebral perfusion pressures than the S-CPR group at the end of ice-cold saline infusion, though the difference was not statistically significant for cerebral perfu-

Table 2. Hemodynamic Characteristics of Groups During Experiment*

Groups	CPR Only (Before Volume Loading)			CPR + Ice-Cold Saline Infusion (After Volume Loading)		
	CoPP	ICP	CePP	CoPP	ICP	CePP
ACD + ITD CPR	43.4 ± 5	29.4 ± 2	37 ± 7	28.3 ± 2	35.4 ± 3	27.6 ± 5
S-CPR	31.2 ± 3	29.3 ± 2	26.8 ± 6	17.4 ± 3†	37.1 ± 3	15.5 ± 5

*All values are expressed in units of mm Hg as mean ± SEM; †$p < 0.05$.
ACD + ITD CPR = active compression-decompression cardiopulmonary resuscitation with impedance threshold device; CePP = cerebral perfusion pressure; CoPP = coronary perfusion pressure; ICP = intracranial pressure; S-CPR = standard cardiopulmonary resuscitation with sham ACD and ITD devices.

sion pressure. Note that sample size was estimated a priori based on expected difference in rate of brain cooling (and not perfusion pressures) between the two groups.

The ice-cold saline infusion resulted in decreased intracranial temperature (°C) in both groups within 1 min after ROSC, significantly lower in the ACD + ITD CPR group (37.6 ± 0.2 to 35.8 ± 0.3) than the S-CPR group (37.8 ± 0.2 to 37.3 ± 0.3, $p < 0.005$) (Fig. 3). The intracranial temperature differences persisted even at 5 min after ROSC. The maximum intracranial temperature decrease was achieved more rapidly in ACD + ITD CPR (by 1 min of ROSC) than S-CPR pigs (by 5 min after ROSC). At 1 min of ROSC (but not at the end of the infusion), the intracranial-to-arterial temperatures gradient was significantly narrower in ACD + ITD CPR (1.6 ± 0.5°C) than S-CPR pigs (5.2 ± 0.5°C, $p < 0.01$) (Fig. 4). There was also a decrease in nasopharyngeal, arterial, and esophageal temperatures with infusion of ice-cold saline in both groups, but the differences were not statistically significant between the groups (Table 3).

Ice-cold saline infusion resulted in decreased thoracic aorta hematocrit in both ACD + ITD CPR (31.4 ± 2% to 19.8 ± 1%, $p < 0.01$) and S-CPR pigs (31.3 ± 1% to 21.1 ± 1%, $p < 0.05$) at infusion end. However, there was no significant hematocrit difference between ACD + ITD CPR (30.4 ± 2%) and S-CPR pigs (28.7 ± 3%) at 5 min after ROSC ($p = 0.4$). Additionally, there were no significant differences in arterial blood gas values between the two groups during or after the saline infusion.

All ACD + ITD CPR pigs (8 of 8, 100%) were defibrillated into a perfusing rhythm that was sustained for at least 15 min without additional intervention. Only 3 of 8 (38%) S-CPR pigs defibrillated to a perfusing rhythm and survived 15 min ($p < 0.05$, Fisher exact test). Additionally, one S-CPR pig had transient ROSC that lasted only 1 min before developing refractory pulseless electrical activity, despite CPR. The remaining four S-CPR pigs were not able to be resuscitated and were excluded. There were no clinical observations consistent with pulmonary edema or mechanical complications in either group. The average number of attempted defibrillation shocks required for ACD + ITD CPR (1.5 ± 0.3) was less than for S-CPR (2.3 ± 0.3, $p = 0.03$).

DISCUSSION

This study demonstrated the feasibility of using mechanical CPR adjuncts in conjunction with large volume ice-cold saline infusion to rapidly cool the brain during CA. For the first time, this study demonstrated that cerebral cooling is more rapid when ACD + ITD CPR, rather than well-performed S-CPR, is combined with rapid IV infusion of ice-cold saline *during* CA. Previous studies in animals and humans have established that ACD + ITD CPR results in negative intrathoracic pressure during the decompression phase, which enhances blood return to the heart, cardiopulmonary circulation, and survival outcomes (15–19). These results support a conclusion that the more efficient circula-

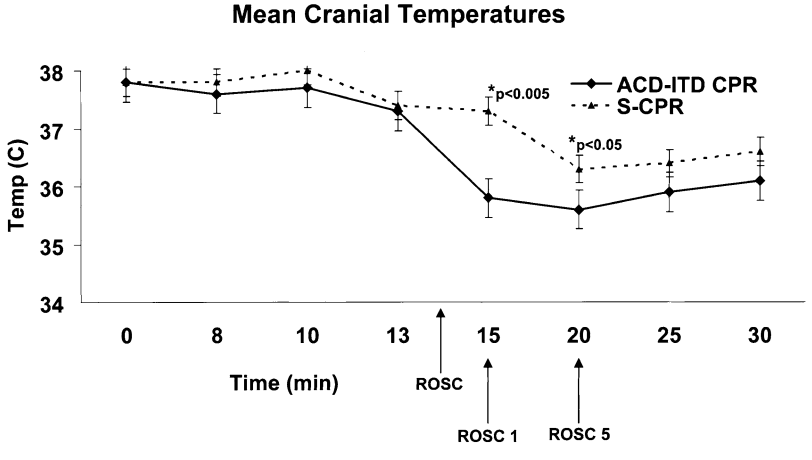

Figure 3. Comparison of brain temperatures for active compression-decompression plus an inspiratory impedance threshold device cardiopulmonary resuscitation (ACD-ITD CPR) versus standard cardiopulmonary resuscitation (S-CPR) groups. ROSC = return of spontaneous circulation.

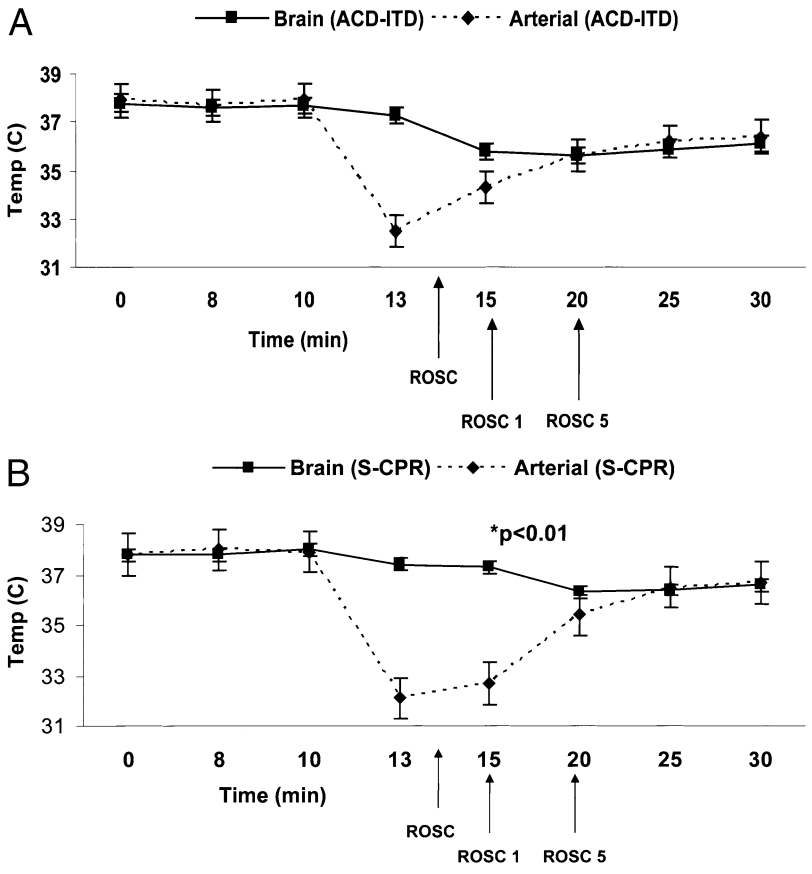

Figure 4. Comparison of brain and arterial blood temperature curves between active compression-decompression plus impedance threshold device cardiopulmonary resuscitation (ACD-ITD CPR) and standard cardiopulmonary resuscitation (S-CPR). **(A)** Brain and arterial temperatures in ACD-ITD CPR. **(B)** Brain and arterial temperatures in S-CPR.

tion of the ice-cold saline infusion by ACD + ITD CPR improved the rapidity of cooling. In the current study, the right atrial pressures in S-CPR pigs were significantly higher than ACD + ITD CPR pigs. This suggests that infusate congested the right heart with S-CPR. Additional support for improved circulation with ACD + ITD CPR is the significantly narrower gradient between the intracranial and arterial temperatures at 1 min of ROSC in ACD + ITD CPR (1.6 ± 0.5°C) versus S-CPR pigs (5.2 ± 0.5°C, $p < 0.01$) (Fig. 4).

The rate of cerebral cooling achieved by ACD + ITD CPR in our study (0.44°C/min) is comparable or superior to that achieved in other experimental studies that have employed a variety of advanced techniques (1–3,10,20–27) (Table 4). Rapid infusion of large volume ice-cold IV fluid has been studied in healthy volunteers (25,26) and elective surgical patients (27). More recently, rapid infusion of 30 ml/kg of ice-cold (4°C) lactated Ringer's solution over 30 min *after* ROSC significantly decreased median core temperature from 35.5°C to 33.8°C in survivors of out-of-hospital CA (10). However, the efficacy of this technique has not been studied *during* CA (active CPR). Our study confirms the efficacy of inducing hypothermia rapidly using this technique when employed during CA as demonstrated by a decrease in intracranial temperature in both the ACD + ITD CPR group and the S-CPR group by 1 min

Table 3. Comparison of Cooling at Different Sites of Measurement During Protocol*

	Cerebral			Arterial Blood		
Sites	**Baseline**	**End-Infusion**	**ROSC (1 min)**	**Baseline**	**End-Infusion**	**ROSC (1 min)**
ACD + ITD CPR	37.6 ± 0.2	37.3 ± 0.1	35.8 ± 0.2†	37.9 ± 0.2	32.5 ± 0.7	34.3 ± 0.5
S-CPR	37.8 ± 0.3	37.4 ± 0.3	37.3 ± 0.3	37.8 ± 0.2	32.1 ± 0.6	32.7 ± 0.3
	Esophageal			**Nasopharyngeal**		
ACD + ITD CPR	35.6 ± 0.3	32.4 ± 0.1	32.5 ± 0.3	37.5 ± 0.1	37.1 ± 0.1	36.5 ± 0.2
S-CPR	35.5 ± 0.2	32.9 ± 0.5	32.2 ± 0.1	37.6 ± 0.2	37.2 ± 0.2	37.1 ± 0.4

*All values are expressed in units of °C as mean ± SEM; †$p < 0.05$.

ACD + ITD CPR = active compression-decompression cardiopulmonary resuscitation with impedance threshold device; ROSC = return of spontaneous circulation; S-CPR = standard cardiopulmonary resuscitation with sham ACD and ITD devices.

Table 4. Comparison of Different Cooling Techniques in Humans and Animals

	Authors	Settings	Cooling Techniques	Rate of Cooling, Site of Measurement
Humans	Yanagawa (1)	Out-of-hospital CA survivors	Surface cold air blanket	0.008°C/min, bladder or arterial
	Bernard (2)	Out-of-hospital CA survivors	Surface ice-packs	0.015°C/min, bladder or tympanic
	HACA (3)	Out-of-hospital CA survivors	Surface cold air blanket	0.005°C/min, bladder
	Hachimi-Idrissi (20)	Out-of-hospital CA survivors	Cooling helmet device	0.025°C/min, tympanic
	Bernard (10)	Out-of-hospital CA survivors	Rapid IV ice-cold fluid bolus	0.050°C/min, bladder
	Rajek (25)	Healthy adults	Rapid IV ice-cold fluid bolus	0.083°C/min, tympanic
	Frank (26)	Healthy adults	Rapid IV ice-cold fluid bolus	0.036°C/min, tympanic
	Baumgardner (27)	Elective surgery, adults	Rapid IV ice-cold fluid bolus	0.120°C/min, tympanic
Animals	Behringer (21)	During CA, dogs	Rapid aortic ice-cold fluid bolus	0.610°C/min, tympanic
	Xiao (22)	Post-CA, dogs	Peritoneal cooling	0.300°C/min, tympanic
	Harris (23)	Anesthetized dogs	Pulmonary perfluorocarbon lavage	0.500°C/min, tympanic
	Inderbitzen (24)	Anesthetized pigs	Intravascular catheter	0.100°C/min, intracranial
	Present study	During CA, pigs	Rapid intravenous ice-cold fluid bolus	0.440°C/min, intracranial

CA = cardiac arrest; HACA = Hypothermia After Cardiac Arrest trial; IV = intravenous.

of ROSC. This decrease was short-lived presumably because we did not continue the infusion of ice-cold saline during ROSC. We would expect this decrease in temperature to be sustained if additional cooling technologies such as cooling blankets were applied immediately after ROSC. This finding is very clinically significant because other animal studies suggest that anoxic brain injury might be significantly reduced if hypothermia is induced during or immediately after CA (4–8).

A potential concern with the rapid infusion of large volume saline during CA is volume loading of the ischemic right ventricle. Ditchey and Lindenfield (28) observed that rapid infusion of large volume saline during CA resulted in disproportionate reduction of the average pressure differences generated across the coronary circulation from 11.0 ± 2.5 mm Hg to 3.7 ± 1.3 mm Hg ($p < 0.01$) and cerebral circulation from 16.1 ± 2.3 mm Hg to 10.5 ± 1.5 mm Hg ($p < 0.01$). Similarly, in our study, we observed a reduction in coronary and cerebral perfusion pressures in both groups with rapid large volume saline infusion (Table 2); however, the reduction in coronary and cerebral perfusion was proportionally less in ACD + ITD CPR versus S-CPR pigs. We believe that greater negative intrathoracic pressures generated during ACD + ITD CPR decompression phase results in a greater pressure differential across the coronary and cerebral vascular beds, thus promoting vital organ perfusion in the face of volume loading.

Study limitations. This study was limited by lack of long-term survival or neurologic outcome measures. Tympanic and bladder temperatures were not measured, limiting comparisons with other studies. Additionally, potential harm from volume loading of an ischemic right ventricle remains a concern, even though ACD + ITD CPR resulted in more rapid cooling and better short-term survival. A very important limitation of this study was the lack of additional control groups including ACD + ITD CPR with rapid infusion of saline at 37°C, and S-CPR with and without rapid infusion of saline at 37°C. Consequently, the observed survival benefit in our study may be entirely due to better hemodynamics associated with ACD + ITD CPR, and not necessarily due to more rapid brain cooling.

Conclusions. In this animal model, ACD + ITD CPR, combined with rapid IV ice-cold saline infusion during CA, resulted in more rapid cerebral cooling and higher short-term survival rates when compared with S-CPR. The more effective cooling of brain after ROSC is attributed to more efficient perfusion of cooled blood during ACD + ITD CPR. This suggests that it is feasible to use CPR adjuncts to increase circulation during CPR to achieve hypothermic cerebral protection during and immediately after CA. Based upon these results, further studies are warranted to determine the potential long-term cerebral protective benefits of the combined use of ACD + ITD CPR and induction of hypothermia during CPR.

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