

Intra-arrest rapid head cooling improves postresuscitation myocardial function in comparison with delayed postresuscitation surface cooling

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Objective: To compare resuscitation outcomes and myocardial function among intra-arrest head cooling, delayed surface cooling, and uncooled controls.

Design: Prospective animal study.

Setting: University-affiliated animal research laboratory.

Subjects: Twenty-four male domestic pigs.

Interventions: Ventricular fibrillation remained untreated for 10 mins after which animals were assigned into three groups: 1) intra-arrest head cooling, 2) postresuscitation surface cooling, and 3) uncooled controls. Head cooling by evaporative perfluorochemical began coincident with the start of cardiopulmonary resuscitation and continued for a total of 4 hrs. Surface cooling using a cooling blanket began at 2 hrs after return of spontaneous circulation and continued for 8 hrs. Control animals were treated identically with the exception for cooling.

Measurements and Main Results: Return of spontaneous cir-

ulation was achieved in eight of eight head-cooled animals, in seven of eight surface-cooled animals, and in seven of eight of controls. Myocardial functions measured by transthoracic echocardiography were significantly better in the head-cooled animals than in surface-cooled and controls. All head-cooled animals survived for more than 96 hrs. This contrasted with six of eight survivors after surface cooling, and only two of eight among controls.

Conclusions: Both intra-arrest head cooling and delayed surface cooling improved postresuscitation myocardial dysfunction. The beneficial effects were greatest with head cooling initiated with cardiopulmonary resuscitation. (Crit Care Med 2008; 36[Suppl.]:S434–S439)

KEY WORDS: myocardial function; cardiac arrest; cardiopulmonary resuscitation; return of spontaneous circulation; echocardiography; hypothermia

Therapeutic hypothermia has been known to be beneficial in neurologic outcomes of patients suffering from stroke, traumatic injury, or cardiac arrest (1–5). In addition to neuroprotection, hypothermia protects the cardiomyocyte from ischemia/reperfusion injury (6), and diminishes the

myocardial infarct size in animal models of coronary occlusion (7, 8).

In cardiac arrest, systemic hypothermia initiated after resuscitation has also been shown to improve survival and long-term neurologic outcome (2, 3, 9). Although the impact of systemic cooling on cardiac arrests is recognized, the optimal timing of inducing hypothermia during cardiac arrest remains undetermined. Boddicker et al. (10) demonstrated that moderate or severe systemic hypothermia before resuscitation improved the success of defibrillation and return of spontaneous circulation (ROSC) in a porcine model of cardiac arrest following 8 mins of untreated ventricular fibrillation (VF). In a rat model of cardiac arrest, Abella et al. (11) showed that systemic cooling initiated during the arrest period had a large impact on survival as compared with delayed cooling initiated only 15 mins after ROSC.

Intra-arrest and postresuscitation hypothermia are more practical in treating patients clinically. However, the effect of variable timing of inducing hypothermia on the postresuscitation myocardial function is still largely unknown. Our hypoth-

esis was that rapid head cooling during cardiopulmonary resuscitation (CPR) followed by systemic cooling reduces the severity of postresuscitation myocardial dysfunction over delayed postresuscitation surface cooling after prolonged cardiac arrest. In the present study, we sought to compare the effect of preferential head cooling initiated at the start of CPR, delayed postresuscitation surface cooling and uncooled control on postresuscitation myocardial function and survival.

METHODS

Experiments were performed in an established swine model of cardiac arrest and CPR. 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.

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Animal Preparation. Twenty-four male domestic pigs weighing between 42 ± 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 intravenously injected at intervals of 1 hr to maintain anesthesia. Animals were mechanically ventilated with a volume-controlled ventilator (MA-1, Puritan-Bennett, Carlsbad, CA). End-tidal P_{CO_2} was monitored with an infrared analyzer (01R-7101A, Nihon Kohden Corp., Tokyo, Japan). Respiratory frequency was adjusted to maintain end-tidal P_{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 and pulmonary arterial pressures, and blood temperature, a 7F thermodilution-tipped catheter was advanced from the right femoral vein and flow-directed into the pulmonary artery. Another 5F thermodilution-tipped catheter was placed in the internal jugular vein (5 cm from the insertion point) to measure the head temperature. For measurements of electrocardiogram signal, three adhesive electrodes were applied to the shaved skin of the right upper, and left upper, and lower limbs. For inducing VF, a 5F pacing catheter (EP Technologies Inc., Mountain View, CA) was advanced from the right cephalic vein into the right ventricle. The position of the catheters was confirmed by characteristic pressure morphology and/or fluoroscopy.

Experimental Protocol. Fifteen minutes before inducing cardiac arrest, baseline measurements were obtained. 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. Before starting the resuscitation procedure, the pacing catheter was withdrawn to avoid injury during chest compression. After 10 mins of untreated VF, CPR was started with a pneumatic piston-driven chest compressor (Thumper 1000, Michigan Instruments, Grand Rapids, MI). 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 decrease the anteroposterior diameter by 25%. Coincident with starting precordial compression, the animal was mechanically ventilated with a tidal volume of 15 mL/kg and F_{IO_2} of 1.0. After 2 mins of chest compression, a dose of epinephrine (30 μ g/kg) was injected into the right atrium. After another 3 mins of chest

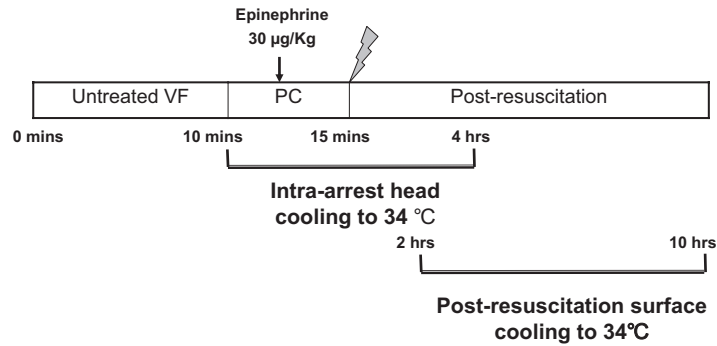


Figure 1. Graphic illustration of the experimental setup. Epinephrine was administered 2 mins after starting precordial compression (PC), and biphasic defibrillation of 150 J was delivered after 5 mins of PC. VF, ventricular fibrillation.

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 mins or more, the animal was regarded as successfully resuscitated. If spontaneous circulation was not restored, CPR was resumed for 1 min before the next defibrillation attempts. This sequence was repeated until the animal was either successfully resuscitated or pronounced dead after a total of 15 mins of CPR. After successful resuscitation, the animals were monitored in an intensive care setting for an additional 10 hrs (Fig. 1). The jugular and core temperatures, electrocardiogram, aortic pressure, right atrial pressure, and pulmonary artery pressure were continuously monitored as previously described (12–14). Cardiac output and echocardiographic measurements were obtained hourly during the first 4 hrs. The animals were then returned to their cages and observed for an additional 86 hrs. At 96 hrs, animals were reanesthetized with ketamine and pentobarbital, and echocardiographic measurements were repeated. After the final measurement, the animals were killed with an intravenous injection of 150 mg/kg pentobarbital. Autopsy was performed on all animals.

Induction of Hypothermia. The experimental animals were equally divided into three treatment groups: 1) intra-arrest head cooling, 2) postresuscitation surface cooling, and 3) uncooled control. Before the onset of cardiac arrest, the core temperature of all the animals was kept at 38°C by using warm or cold water bags. In the intra-arrest cooling group, head cooling was induced by using the Rhinochill (Benechill Inc, San Diego, CA) nasal catheter system. The Rhinochill device sprays a liquid perfluorochemical 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 predominantly hematogenously, through the submucosal nasal venous plexuses and also by direct convection. Body cool-

ing occurs later. The intranasal catheters were positioned in the animal's nostrils, and perfluorochemical was delivered at 1 mL/kg/min with oxygen at 1 L/kg/min. The cooling was initiated at the same time as precordial compression and stopped once core temperature reached 34°C or at 4 hrs, whichever occurred first. In the delayed postresuscitation group, the surface cooling was induced by Maxi-Therm blankets connected to the Blanketrol Hyper-Hypothermia system (Cincinnati Sub-Zero Products, Cincinnati, OH), at 2 hrs after ROSC. The cooling was stopped once the core temperature reached 34°C or at 10 hrs after resuscitation. Cooling was resumed in the two cooling groups if the core temperature increased to 34.5°C within the respective cooling period. Rewarming was passive. The temperature of the control group was not controlled after induction of VF.

Echocardiographic Measurements. Echocardiographic measurements were obtained with the aid of a S7-20mni, 3.5 MHz transthoracic echocardiographic transducer (HD11XE, Ultrasound System Specification, Philips Medical Systems, Eindhoven, The Netherlands). Transthoracic two-dimensional echocardiography and Doppler studies were performed before VF, hourly for 4 hrs after ROSC, and repeated at the 96th hr after resuscitation. In the view of the short axis, left ventricular end-systolic and end-diastolic volumes were obtained by the method of discs. Left ventricular ejection fractions and fractional area change were then calculated. In the apical four-chamber view, several transmitral flow parameters, including peak E and A transmitral flow velocities, E/A ratio, time interval from cessation to onset of mitral inflow, and the deceleration time of early transmitral flow were measured. Pulmonary venous systolic and diastolic flow velocities and S/D ratio were also obtained by pulsed-wave Doppler. In the apical five-chamber apical view, aortic flow was recorded by using pulsed Doppler with the smallest sample volume placed at the level of the aortic annulus. Left ventricular ejection time was measured from the beginning to end of the aortic flow wave.

The myocardial performance index, which combines time intervals related to systolic and diastolic functions, and reflecting the global cardiac function, was calculated using the formula $(a - b)/b$, where a is mitral closure-to-opening interval (time interval from cessation to onset of mitral inflow); and b is ejection time (aortic flow ejection time, obtained at the left ventricular outflow tract). Higher myocardial performance index is indicative of worse myocardial performance (15, 16). With the use of tissue Doppler echocardiography, the velocities of motion of the mitral annulus were recorded by putting the sample volume at the interventricular septal wall at the level of the mitral annulus (17, 18). The isovolumic relaxation time was measured from aortic valve closure to mitral valve opening by using pulsed Doppler (19).

Statistical Analyses. The Fisher's exact test was used for the comparison of the categorical variables. Continuous variables were presented as mean \pm SD, and analysis of variance was used to check the difference between the groups. Comparisons between time-based measurements within the groups were performed with analysis of variance repeated measurements. A value of $p < .05$ was considered significant. Analyses were carried out using SPSS V.11.0 software (SPSS, Inc, Chicago, IL).

RESULTS

Baseline myocardial function and hemodynamics did not differ significantly among these three groups. At baseline, head and core temperatures were the same in all groups (head: $38.1 \pm 0.3^\circ\text{C}$ in the intra-arrest cooling group, $38.2 \pm 0.2^\circ\text{C}$ in the delayed cooling group, and $38.0 \pm 0.3^\circ\text{C}$ in the control group; core: $38.0 \pm 0.2^\circ\text{C}$ in the intra-arrest cooling group, $38.0 \pm 0.0^\circ\text{C}$ in the delayed cooling group, and $38.0 \pm 0.1^\circ\text{C}$ in the control group).

In the intra-arrest cooling group, head temperature started falling within 1 min of initiation of cooling and CPR. At 5 mins, head temperature was $34.2 \pm 4.5^\circ\text{C}$ in the intra-arrest cooling group compared with $38.3 \pm 0.2^\circ\text{C}$ in the delayed cooling group and $38.1 \pm 0.3^\circ\text{C}$ in the control group (Fig. 2). Thirty minutes after resuscitation, the head temperature was $31.5 \pm 6.9^\circ\text{C}$ and the core temperature was $37.0 \pm 0.5^\circ\text{C}$ in the intra-arrest cooling group. In the delayed cooling group, the core temperature reached 37°C after 4.5 hrs following ROSC. Seven of the eight animals in the intra-arrest cooling group achieved a core temperature of 34°C within the 4-hr period. The average time to target core temperature in the intra-arrest cooling group was 55.4 ± 73.8 mins ($n = 7$). In contrast, only five of the eight animals in the de-

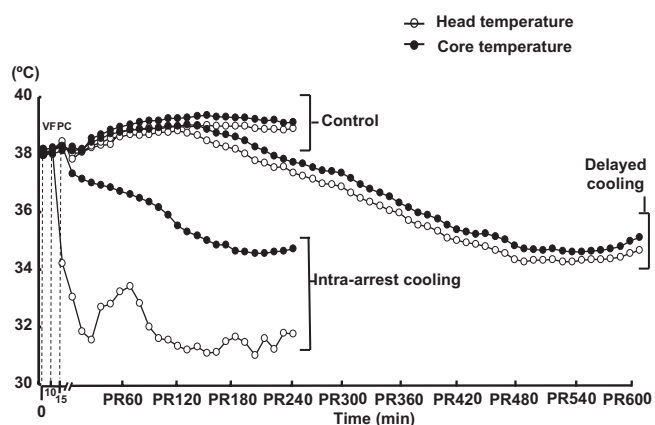


Figure 2. Head and core temperatures of experimental groups. BL, baseline; PC, precordial compression; PR, postresuscitation; VF, ventricular fibrillation.

Table 1. Resuscitation between experimental groups

| | Control n = 8 | Intra-Arrest Cooling n = 8 | Delayed Cooling n = 8 | p^a | | |
|--|-------------------|----------------------------------|-----------------------------|-------|-------|-------|
| | | | | C & I | C & D | I & D |
| Body weight (kg) | 40.8 \pm 1.9 | 40.4 \pm 0.7 | 41.1 \pm 3.7 | 0.613 | 0.797 | 0.576 |
| CPR duration (sec) | 612.9 \pm 227.3 | 364.6 \pm 42.4 | 422.4 \pm 201.1 | 0.017 | 0.132 | 0.438 |
| Epinephrine dosage ($\mu\text{g}/\text{kg}$) | 60 \pm 32.1 | 30 \pm 0 | 42 \pm 31.8 | 0.019 | 0.260 | 0.334 |
| CPP before initial electrical shock (mm Hg) | 17.7 \pm 5.6 | 21.3 \pm 9.6 | 19.6 \pm 7.94 | 0.370 | 0.581 | 0.705 |
| Total shock number | 14.8 \pm 8.8 | 8.1 \pm 4.6 | 5.5 \pm 3.3 | 0.073 | 0.015 | 0.211 |
| Initial shock success (%) | 38 | 75 | 63 | 0.315 | 0.619 | 1.000 |
| Total shock success (%) | 66 \pm 19 | 88 \pm 18 | 74 \pm 34 | 0.034 | 0.587 | 0.319 |
| ROSC | 7 (88%) | 8 (100%) | 7 (88%) | 1.000 | 1.000 | 1.000 |
| Survival for 96 hrs | 2 (25%) | 8 (100%) | 5 (63%) | 0.003 | 0.315 | 0.200 |

I, intra-arrest cooling; D, delayed cooling; C, control; CPP, coronary perfusion pressure; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

^a $p < 0.05$ was considered significant.

layed cooling group achieved a core temperature of 34°C within the cooling period. The average time to target core temperature in the delayed cooling group was 442 ± 49.7 mins ($n = 5$).

Compared with the control group, fewer defibrillation shocks were required to achieve ROSC in the intra-arrest cooling group (8.1 ± 4.6 vs. 14.8 ± 8.8 , $p = .073$) and the delayed cooling group (5.5 ± 3.3 vs. 14.8 ± 8.8 , $p = .015$). There was no difference in the number of defibrillation shocks between the intra-arrest cooling group and delayed cooling group. The success rate for total shocks than the control group ($88 \pm 18\%$ vs. $66 \pm 19\%$, $p = .034$) but not for initial shocks (75% vs. 38% , $p = .315$). There was no difference in success of total shocks nor initial shock between the intra-arrest cooling group and delayed cooling group. The total dose of epinephrine required was also lower in the intra-arrest cooling group ($30 \pm 0 \mu\text{g}/\text{g}$ vs. $60 \pm 32.1 \mu\text{g}/\text{kg}$,

$p = .009$) as was the duration of CPR (364.6 ± 42.4 sec vs. 600.4 ± 243.2 sec, $p = .01$) when compared with the control group but not the delayed cooling group (Table 1).

ROSC was achieved in eight of eight (100%) in the intra-arrest cooled animals, in seven of eight in the delayed cooled animals (88%), and in seven of eight in controls (88%) ($p = \text{NS}$). Coronary perfusion pressure before initial defibrillation was 21.3 ± 9.6 mm Hg in the intra-arrest cooling group, 19.6 ± 7.94 mm Hg in the delayed cooling group, and 17.7 ± 5.6 mm Hg in the controls ($p = \text{NS}$).

When left ventricular ejection fraction decreased from $64.8 \pm 3.6\%$ to $56.3 \pm 3.8\%$ in the intra-arrest cooled animals during the first hour after cardiac arrest, left ventricular ejection fraction decreased from $62.6 \pm 2.3\%$ to $50.8 \pm 3.4\%$ in the delayed cooled animals ($p = .017$) and from $63.9 \pm 3.7\%$ to $49.7 \pm 3.7\%$ in the controls ($p = .005$). Four hours after resuscitation, it was $63.5 \pm 2.2\%$ in the

intra-arrest cooling group, $52.4 \pm 3.3\%$ in the delayed cooling group, and $51.2 \pm 4.7\%$ in the control group (Fig. 3). At 96 hrs, left ventricular ejection fraction had returned to baseline value in the intra-arrest cooling group, but remained 5% below baseline in the delayed cooled animals ($p = .023$), and 11% below baseline in the controls ($p = .003$). Within 1 hr after resuscitation, fractional area change decreased from $50.1 \pm 3.4\%$ to $40.5 \pm 3.8\%$ in the intra-arrest cooling group compared with $47.7 \pm 2.8\%$ to $35.3 \pm$

4.3% in the delayed cooling group ($p = .034$), and $49.4 \pm 4.0\%$ to $33.5 \pm 5.1\%$ in the control group ($p = .010$). At 4 hrs after resuscitation, it recovered to $48.7 \pm 3.0\%$ in the intra-arrest cooling group, $38.5 \pm 5.8\%$ in the delayed cooling group, and $36.6 \pm 4.2\%$ in the control group (Fig. 3). The heart rate of the intra-arrest cooled animals showed a significant difference from the delayed cooling group from 2 hrs to 4 hrs after resuscitation, and from the control during 4 hrs after resuscitation. During this period of postresuscitation 4 hrs, the blood pressure did not show a significant difference among these three groups (Table 2).

The isovolumic relaxation time decreased in all of the groups after resuscitation and recovered during the remainder of the 4-hr observation period. The intra-arrest cooled animals recovered faster than the delayed cooled and control animals (Fig. 4). The E/E' ratio, a parameter of diastolic function, increased to >10 in all the groups after ROSC and decreased thereafter. The intra-arrest cooled animals had significantly lower E/E' ratios than the delayed cooled animals from 2 to 3 hrs after resuscitation, and controls beyond the first hour after resuscitation (Fig. 4). Furthermore, the deceleration time of early transmitral flow, pulmonary venous flow S/D ratio,

and myocardial performance index also improved faster in the intra-arrest cooled animals compared with both the delayed cooling group and control group. There was no difference in E/A ratio among these three groups (Table 2).

All eight intra-arrest cooled animals survived to 96 hrs (100%). In contrast, only five of the delayed cooled animal (63%, $p = .200$) and two of the controls that were successfully resuscitated survived to this time point (25%, $p = .003$ vs. intra-arrest cooling group, $p = .315$ vs. delayed cooling group).

DISCUSSION

The results of the current study demonstrated that both intra-arrest cooling and delayed postresuscitation cooling improved postresuscitation myocardial dysfunction, and the beneficial effect was more significant when cooling was initiated at the beginning of CPR.

In a porcine cardiac arrest model, Boddicker et al. (10) showed systemic hypothermia established before cardiac arrest improved the defibrillation success and resuscitation outcome suggesting that hypothermia may be beneficial to the resuscitation efforts. Intra-arrest systemic hypothermia has also been shown to reduce mortality rates in rats (11) and

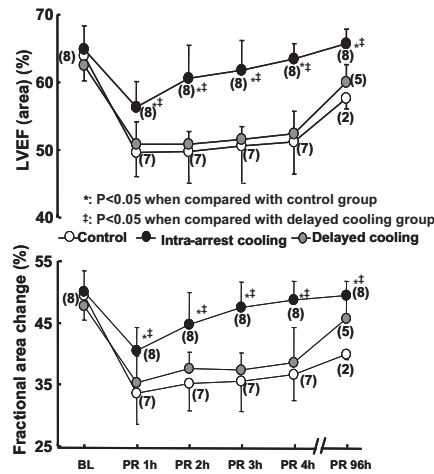


Figure 3. Left ventricular ejection fraction (LVEF) and fractional area change of experimental groups. BL, baseline; PR, postresuscitation.

Table 2. Hemodynamic and echocardiographic measurements between experimental groups

| | Baseline | PR 1 hr | PR 2 hr | PR 3 hr | PR 4 hr | PR 96 hr |
|----------------------|--------------|----------------------------|----------------------------|-----------------------------|-----------------------------|----------------------------|
| HR (min) | | | | | | |
| Intra-arrest cooling | 104.0 ± 13.5 | 157.5 ± 36.5 ^a | 135.8 ± 23.9 ^b | 136.3 ± 24.8 ^{b,c} | 134.5 ± 24.7 ^{b,d} | 109.1 ± 25.5 |
| Delayed cooling | 106.1 ± 13.6 | 176.7 ± 18.9 ^a | 182.0 ± 24.5 | 181.8 ± 17.4 ^a | 167.3 ± 19.5 ^b | 123.2 ± 20.1 |
| Control | 119.8 ± 21.4 | 205.3 ± 18.6 | 209.0 ± 23.2 | 207.0 ± 8.3 | 215.4 ± 23.5 | 144.0 ± 33.9 |
| MAP (mm Hg) | | | | | | |
| Intra-arrest cooling | 115.5 ± 12.1 | 103.5 ± 9.7 | 108.8 ± 15.2 | 120.3 ± 12.4 | 125.8 ± 14.5 | NA |
| Delayed cooling | 124.1 ± 9.2 | 110.0 ± 7.9 | 120.6 ± 8.8 | 128.4 ± 13.2 | 126.6 ± 6.4 | NA |
| Control | 122.9 ± 13.6 | 113.3 ± 14.9 | 123.3 ± 18.1 | 122.4 ± 13.1 | 122.0 ± 12.4 | NA |
| E/A | | | | | | |
| Intra-arrest cooling | 1.32 ± 0.06 | 1.23 ± 0.16 ^d | 1.24 ± 0.16 ^d | 1.30 ± 0.15 | 1.30 ± 0.15 ^d | 1.32 ± 0.09 |
| Delayed cooling | 1.12 ± 0.09 | 1.438 ± 0.188 | 1.51 ± 0.25 | 1.49 ± 0.14 | 1.63 ± 0.23 ^a | 1.35 ± 0.13 |
| Control | 1.35 ± 0.09 | 1.25 ± 0.41 | 1.37 ± 0.27 | 1.46 ± 0.22 | 1.46 ± 0.22 | 1.18 ± 0.08 |
| DT (sec) | | | | | | |
| Intra-arrest cooling | 0.13 ± 0.02 | 0.07 ± 0.01 ^a | 0.09 ± 0.02 ^a | 0.10 ± 0.01 ^{b,d} | 0.11 ± 0.02 ^a | 0.14 ± 0.02 ^a |
| Delayed cooling | 0.13 ± 0.01 | 0.08 ± 0.01 | 0.08 ± 0.01 | 0.08 ± 0.01 ^a | 0.09 ± 0.01 ^a | 0.14 ± 0.02 ^a |
| Control | 0.11 ± 0.02 | 0.06 ± 0.01 | 0.07 ± 0.01 | 0.07 ± 0.01 | 0.07 ± 0.01 | 0.09 ± 0.01 |
| S/D | | | | | | |
| Intra-arrest cooling | 1.08 ± 0.05 | 0.80 ± 0.12 ^c | 1.06 ± 0.08 ^b | 1.07 ± 0.06 ^{bb} | 1.07 ± 0.06 ^d | 1.07 ± 0.05 |
| Delayed cooling | 1.12 ± 0.09 | 0.83 ± 0.05 | 0.84 ± 0.05 | 0.91 ± 0.10 | 1.02 ± 0.10 ^a | 1.07 ± 0.03 |
| Control | 1.05 ± 0.03 | 0.80 ± 0.07 | 0.83 ± 0.07 | 0.90 ± 0.07 | 1.02 ± 0.10 | 1.04 ± 0.08 |
| MPI | | | | | | |
| Intra-arrest cooling | 0.52 ± 0.03 | 0.69 ± 0.06 ^{a,d} | 0.63 ± 0.08 ^{a,c} | 0.56 ± 0.05 ^{a,c} | 0.52 ± 0.01 ^{b,c} | 0.52 ± 0.03 ^{a,d} |
| Delayed cooling | 0.63 ± 0.22 | 35.26 ± 4.32 | 37.62 ± 2.62 | 37.35 ± 2.83 | 38.51 ± 5.77 | 45.72 ± 3.32 |
| Control | 0.51 ± 0.03 | 0.91 ± 0.24 | 0.90 ± 0.23 | 0.88 ± 0.32 | 0.78 ± 0.07 | 0.65 ± 0.13 |

DT, decelerating time; HR, heart rate; MAP, mean arterial pressure; MPI, myocardial performance index; NA, not available; PR, postresuscitation; S/D, systolic/diastolic.

^a $p < 0.05$; ^b $p < 0.005$ when compared with control group; ^c $p < 0.001$ when compared with delayed cooling group; ^d $p < 0.05$.

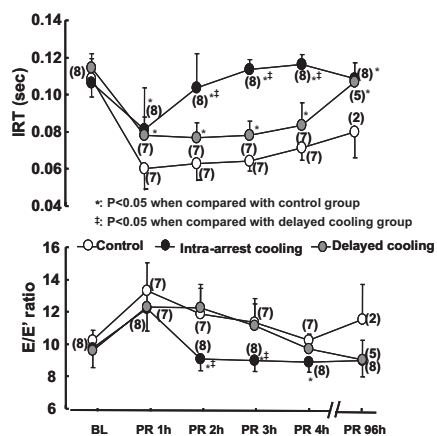


Figure 4. Isovolumic relaxation time (*IRT*) and mitral annulus *E/E'* ratio of experimental groups. *BL*, baseline; *PR*, postresuscitation.

enable neurologic intact survival in dogs (9). In the current study, the intra-arrest cooling group had a shorter CPR duration, fewer epinephrine dosages and lower total shock success rate compared with control but not the delayed cooling group, and the delayed cooling group had fewer numbers of shocks when compared with control. Because the experimental animals were randomized into the intra-arrest cooling group and control group, it is reasonable to deduce that intra-arrest cooling may facilitate resuscitation. The delayed cooling group and the control should have similar resuscitation events if the delayed cooled animals were also randomized. The study of the delayed group was executed after the finish of both the intra-arrest cooling group and control group. Therefore, a learning experience may have contributed to the improved resuscitation effort of the delayed cooled animals compared with control.

In a rat model of cardiac arrest, Abella et al. (11) previously demonstrated that systemic cooling initiated during the arrest period had a beneficial impact on survival compared with delayed cooling initiated only 15 mins after ROSC. In this study, we also demonstrated that head cooling initiated at the start of CPR significantly improved survival compared with controls. Although all but one animal in the control group achieved ROSC (seven of eight), only two of them survived to 24 hrs, compared with all eight animals in the intra-arrest cooling group. But, there is no statistical difference in survival between the intra-arrest cooling group and the delayed cooling group (five of seven successfully resuscitated animals survived to 24 hrs), and between the de-

layed cooling group and the control group. The limited number of experimental animals in each group restricted the power of statistical analyses. There could be three possible existing conditions. First, if the intra-arrest cooled animals had a better survival rate than the delayed cooled animals, and the delayed cooled animals had better survival rate than the control, we could assume that cooling, including that induced during intra-arrest and postresuscitation period, can improve survival, and the timing of inducing hypothermia would affect survival after cardiac arrest. Second, if the intra-arrest cooling group and the delayed cooling group had the same survival outcome, the timing of inducing hypothermia did not play a crucial role in determining survival after cardiac arrest. The last assumptive condition is that if the delayed cooled animals and control animals had equal survival, which was worse than that of the intra-arrest cooled animals, then only cooling induced during CPR would benefit survival. In the current study, it is difficult to conclude whether intra-arrest cooling improved survival over postresuscitation cooling or postresuscitation cooling benefited survival.

In addition to facilitating resuscitation and improving survival, intra-arrest head cooling also appears to reduce both postresuscitation systolic and diastolic myocardial dysfunctions as compared with the controls. However, postresuscitation systemic cooling merely showed better recovery of diastolic function but not systolic function compared with control. Because there was no difference in resuscitation effort between intra-arrest head cooling group and postresuscitation surface cooling group, myocardial damage resulting after resuscitation cannot totally explain the reason for the intra-arrest head-cooled animals to have better recovery of myocardial systolic dysfunction than did the postresuscitation surface-cooled ones. The difference in the extent of recovery of myocardial systolic dysfunction may result from the difference in the extent of decreased metabolic demand in the myocardium at risk. Therapeutic hypothermia significantly decreased the core temperature after ROSC, and this decreased the heart rate and cellular energy requirements (20). In the animal models, hypothermia has been shown to preserve myocardial adenosine triphosphate stores during ischemia (21, 22). Our results suggested two important fac-

tors of cooling affecting the protective effect of hypothermia in the systolic myocardial function: timing and rate of inducing hypothermia. The intra-arrest cooled animals were cooled using the Rhinocill device, which decreased temperature faster than the cooling blanket. The cooling of the intra-arrest cooling group was initiated coincident with the start of CPR; the cooling of the delayed cooling group was begun 2 hrs after resuscitation. Our current results cannot demonstrate whether the timing, or the rate, or both of inducing hypothermia plays the critical role in the myocardial protection caused by cooling. More extensive studies are necessary to further investigate the optimal timing and appropriate rate of inducing hypothermia.

In the current study, the postresuscitation systemically cooled animals showed better recovery from diastolic dysfunction than the controls. However, it is still undetermined whether the postresuscitation systemic cooling helps recovery from myocardial diastolic dysfunction. Because of the learning effect, the postresuscitation cooled animals suffered from less myocardial damage compared with controls. Further randomization studies should be conducted to clarify the true effect of postresuscitation cooling on postresuscitation myocardial function, including different rates of inducing hypothermia.

There are several limitations to our study. First, only 16 of the studied animals were randomized to the intra-arrest head cooling group and the control group equally. The experiments of the postresuscitation surface-cooled animals were executed after the conclusion of the experiments of the above two groups. A learning effect may exist and affect the results. Second, we used a high jugular venous temperature as a surrogate for head temperature and pulmonary artery temperature for myocardial temperature. We cannot rule out the possibility that at least some of the cooling occurred in the neck rather than the head and that any alteration in sympathetic input to the heart may have resulted from local cooling of the neck. Finally, the study was not blinded. It is difficult to blind the investigators in the study since touching the animals during the experiments allowed the investigators to differentiate between the hypothermic and the control groups. We attempted to account for this by fixing chest compression and ventilation rates. Chest compression was performed by the

Thumper device and there was no difference in coronary perfusion pressure among these three groups during resuscitation.

We concluded that both intra-arrest head cooling and delayed postresuscitation surface cooling improved myocardial function after cardiac arrest. The beneficial effects on the heart were greatest when head cooling was initiated coincident with the start of CPR.

REFERENCES

1. Kim F, Olsufka M, Carlbom D, et al: Pilot study of rapid infusion of 2 L of 4°C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005; 112:715–719
2. The Hypothermia After Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549–556
3. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563
4. Schwab S, Schwarz S, Spranger M, et al: Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke* 1998; 29:2461–2466
5. Fritz HG, Bauer R: Secondary injuries in brain trauma: Effects of hypothermia. *J Neurosurg Anesthesiol* 2004; 16:43–52
6. Shao ZH, Chang WT, Chan KC, et al: Hypothermia-induced cardioprotection using extended ischemia and early reperfusion cooling. *Am J Physiol Heart Circ Physiol* 2007; 292:H1995–H2003
7. Dave RH, Hale SL, Kloner RA: Hypothermic, closed circuit pericardio-perfusion: A potential cardioprotective technique in acute regional ischemia. *J Am Coll Cardiol* 1998; 31:1667–1671
8. Tissier R, Hamanaka K, Kuno A, et al: Total liquid ventilation provides ultra-fast cardioprotective cooling. *J Am Coll Cardiol* 2007; 49:601–605
9. Nozari A, Safar P, Stezoski SW, et al: Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006; 113:2690–2696
10. Boddicker KA, Zhang Y, Zimmerman MB, et al: Hypothermia improves defibrillation success and resuscitation outcomes from ventricular fibrillation. *Circulation* 2005; 111:3195–3201
11. Abella BS, Zhao D, Alvarado J, et al: Intra-arrest cooling improves outcomes in a murine cardiac arrest model. *Circulation* 2004; 109:2786–2791
12. Tang W, Weil MH, Sun S, et al: The effects of biphasic and conventional monophasic defibrillation on post resuscitation myocardial function. *J Am Coll Cardiol* 1999; 34:815–822
13. Tang W, Weil MH, Sun S, et al: A comparison of biphasic and monophasic waveform defibrillation after prolonged ventricular fibrillation. *Chest* 2001; 120:948–954
14. Tang W, Weil MH, Schock RB, et al: Phased chest and abdominal compression-decompression: A new option for cardiopulmonary resuscitation. *Circulation* 1997; 95:1335–1340
15. Tei C: New non-invasive index for combined systolic and diastolic ventricular function. *J Cardiol* 1995; 26:135–136
16. Palmieri V, Okin PM, de Simone G, et al: Electrocardiographic characteristics and metabolic risk factors associated with inappropriately high left ventricular mass in patients with electrocardiographic left ventricular hypertrophy: The LIFE Study. *J Hypertens* 2007; 25:1079–1085
17. Dokainish H: Tissue Doppler imaging in the evaluation of left ventricular diastolic function. *Curr Opin Cardiol* 2004; 19:437–441
18. Huang CH, Tsai MS, Hsieh CC, et al: Diagnostic accuracy of tissue Doppler echocardiography for patients with acute heart failure. *Heart* 2006; 92:1790–1794
19. Chang WT, Ma MH, Chien KL, et al: Post-resuscitation myocardial dysfunction: Correlated factors and prognostic implications. *Intensive Care Med* 2007; 33:88–95
20. Kataoka K, Yanase H: Mild hypothermia—a revived countermeasure against ischemic neuronal damages. *Neurosci Res* 1998; 32:103–117
21. Carrier M, Tourigny A, Thoribé N, et al: Effects of cold and warm blood cardioplegia assessed by myocardial pH and release of metabolic markers. *Ann Thorac Surg* 1994; 58:764–767
22. Ning XH, Xu CS, Song YC, et al: Hypothermia preserves function and signaling for mitochondrial biogenesis during subsequent ischemia. *Am J Physiol* 1998; 274:H786–H793