

## Intra-Cardiopulmonary Resuscitation Hypothermia With and Without Volume Loading in an Ischemic Model of Cardiac Arrest

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**Background**—We investigated the effects of intra-cardiopulmonary resuscitation (CPR) hypothermia with and without volume loading on return to spontaneous circulation and infarction size in an ischemic model of cardiac arrest.

**Methods and Results**—Using a distal left anterior descending artery occlusion model of cardiac arrest followed by resuscitation with a total of 120 minutes of occlusion and 90 minutes of reperfusion, we randomized 46 pigs into 5 groups and used myocardial staining to define area at risk and myocardial necrosis. Group A had no intervention. Immediately after return of spontaneous circulation, group B received surface cooling with cooling blankets and ice. Group C received intra-CPR 680±23 mL of 28°C 0.9% normal saline via a central venous catheter. Group D received intra-CPR 673±26 mL of 4°C normal saline followed by surface cooling after return of spontaneous circulation. Group E received intra-CPR and hypothermia after return of spontaneous circulation with an endovascular therapeutic hypothermia system placed in the right atrium and set at a target of 32°C. Intra-CPR volume loading with room temperature (group C) or iced saline (group D) significantly ( $P<0.05$ ) decreased coronary perfusion pressure (group C, 12.8±4.78 mm Hg; group D, 14.6±9.9 mm Hg) compared with groups A, B, and E (20.6±8.2, 20.1±7.8, and 21.3±12.4 mm Hg). Return of spontaneous circulation was significantly improved in group E (9 of 9) compared with groups A plus B and C (10 of 18 and 1 of 8). The percent infarction to the area at risk was significantly reduced with intra-CPR hypothermia in groups D (24.3±4.2%) and E (4±3.4%) compared with groups A (72±5.1%) and B (67.3±4.2%).

**Conclusions**—Intra-CPR hypothermia significantly reduces myocardial infarction size. Elimination of volume loading further improves outcomes. (*Circulation*. 2009;120:1426-1435.)

**Key Words:** cardiopulmonary resuscitation ■ heart arrest ■ hypothermia ■ infarction ■ resuscitation

Sudden cardiac death is the No. 1 cause of death in the United States, claiming >500 000 lives each year.<sup>1,2</sup> Acute coronary syndromes are the most common cause of this clinical presentation,<sup>3-6</sup> and prolonged acute coronary occlusion causes myocardial necrosis. Hypothermia has been associated with a significant decrease in myocardial infarction size<sup>7-10</sup> and microvascular dysfunction.<sup>11</sup> However, 2 randomized clinical trials failed to show positive results with hypothermia as an adjunct therapy to primary coronary intervention in patients with acute myocardial infarction.<sup>12-14</sup> In subgroup analysis, the patients who reached a temperature of <35°C before reperfusion and had significant anterior wall myocardial infarction showed a reduction in infarct size, suggesting the benefit of inducing hypothermia before reperfusion.

### Clinical Perspective on p 1435

Patients with cardiac arrest caused by coronary occlusion or myocardial ischemia, when identified by rescuers, offer the unique opportunity to apply hypothermia early in the disease process to limit myocardial infarction evolution. It has been shown in animals that early application of hypothermia results in a larger benefit<sup>15-17</sup> and that mild to moderate hypothermia facilitates transthoracic defibrillation.<sup>18</sup> In addition, the therapeutic value of postresuscitation mild to moderate hypothermia for enhancing neurologically intact survival in comatose survivors of cardiac arrest has been established with 2 randomized, controlled trials.<sup>19,20</sup>

The earliest that hypothermia can be applied clinically is with the initiation of cardiopulmonary resuscitation (CPR).

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An easy way to initiate hypothermia is with intravenous administration of ice-cold saline. The effects of intra-CPR cold saline infusion in neurological outcomes have been investigated by Nozari et al<sup>16</sup> and showed dramatic improvement in neurologically intact survival in animals. Recently, Abella et al<sup>17</sup> showed that achieving target hypothermic temperature during CPR is beneficial even if it delays return to spontaneous circulation (ROSC) in a murine model of cardiac arrest. In addition, Staffey et al<sup>21</sup> showed that cold perfluorocarbon ventilation facilitates ROSC.

We hypothesize that intra-CPR hypothermia with or without fluid volume infusion should enhance ROSC, decrease the size of myocardial infarction, and improve postresuscitation left ventricular (LV) function in an ischemic model of cardiac arrest and resuscitation.

## Methods

### Preparation

Studies were approved and performed at Johns Hopkins University. A total of 46 pigs (weight,  $28 \pm 2$  kg) received ketamine 22 mg/kg IM. After endotracheal intubation and mechanical ventilation initiation, anesthesia was maintained with isoflurane (1% to 2.5%) in 100% oxygen. Pigs were placed in the supine position, and using bilateral femoral arterial and venous percutaneous 8F sheath insertions, we placed pigtail catheters under fluoroscopic guidance in the right atrium and ascending aorta. Thermocouples were inserted through the two 8F pigtail catheters and placed at the distal tip for continuous recording of blood temperature and pressure. In addition, a third thermocouple was inserted under fluoroscopic guidance into the cranial continuation of the internal jugular vein (transverse sinus). Tympanic temperature was also measured every 5 minutes after CPR was started. From a left femoral arterial 5F sheath, a 5F pigtail catheter was placed into the LV when needed for ventricular angiographic evaluation of LV systolic function. Normal saline was given intravenously to maintain a mean right atrial pressure of 3 to 5 mm Hg during the preparation phase.

Unfractionate heparin (100 U/kg IV) was given as a bolus after sheath placement was complete. That bolus was followed by 1000-U/h boluses.

Ventilation was delivered at 12 to 14 breaths per minute with a tidal volume of 10 mL/kg. The rate was adjusted to an  $\text{ETCO}_2$  of 38 to 42 mm Hg. An arterial blood gas sample was used to verify baseline conditions.

A baseline left ventriculogram was performed in all animals at a 50° right anterior oblique and 10° caudal projection and a 45° left anterior oblique and 30° cranial projection to assess global LV ejection fraction. Ventriculograms (dye volume, 24 mL at 8 mL/s) and LV end-diastolic pressures (LVEDPs) were also obtained at 30 and 110 minutes after resuscitation in all survivors. LV ejection fraction was evaluated by a blinded independent angiographer. Angiographic planimetry of the 2 orthogonal angiographic projections at end systole and end diastole was used for ejection fraction evaluation.<sup>22</sup>

Under fluoroscopic guidance, a 6F short AL 0.75 guide catheter engaged the left main artery. Using a nonhydrophilic 0.014-in guidewire, we advanced an over-the-wire 2.75×8-mm balloon into the left anterior descending coronary artery (LAD) and placed it after the second diagonal or in the last third of the vessel as seen at a 90° left anterior oblique projection if no second diagonal was identified. (The position was decided on the basis of preliminary experiments. Occlusion at the first diagonal or at the proximal LAD resulted in detrimental insult and an inability to resuscitate the animals from cardiac arrest.) Continuous limb and 2 precordial ECG tracings were recorded.

An additional intravascular catheter was placed in 9 animals (group E; see below). A braided balloon catheter was inserted through a 12F right femoral venous sheath. The distal tip of the

catheter was placed under fluoroscopic guidance into the superior vena cava, and the main part of the body of the catheter was placed into the right atrium for maximization of heat exchange of venous return. The catheter was connected to a hypothermia device (endovascular therapeutic hypothermia system [ETHS], Radiant Medical, Redwood City, Calif)<sup>13</sup> that had a thermocouple to input feedback and to maintain body temperature at 32°C. The thermocouple was placed in the transverse sinus, which was used as the target temperature similar to all other groups. When the venous temperature was  $>32^\circ\text{C}$ , the device was maximizing heat exchange. In this group of animals, right ventricular instead of right atrial temperature was measured to allow for blood mixing and to avoid accidentally measuring the temperature of the catheter.

### Protocol Description

Once baseline parameters were established, the LAD balloon was inflated to 6 atm, and the obstruction was documented with a coronary injection and cineangiography. In addition, ECG confirmation of ST elevation in the precordial and left limb leads was required for the study to be included in the analysis. The position was marked on the screen for further reference. After 15 minutes of occlusion, if animals did not develop spontaneous ventricular fibrillation, delivery of 60-Hz AC current applied to a right ventricular ablation catheter induced ventricular fibrillation (only 2 of the 46 animals developed spontaneous ventricular fibrillation within 15 minutes). At that moment, ventilations and anesthesia were turned off. Five minutes of untreated ventricular fibrillation was followed by 5 minutes of vest CPR,<sup>23</sup> with compressions set at 80 per minute (maximum device rate) and ventilations at 10 per minute (10-mL/kg tidal volume) with 100% oxygen asynchronously with the chest compressions. Vest CPR has been shown to optimize blood flow to the heart and brain compared with standard manual CPR and was chosen to deliver consistent and good-quality compressions to minimize manual compression variability and potential bias. In addition, coronary angiography is feasible through the vest, and full visualization of the coronary tree is possible.

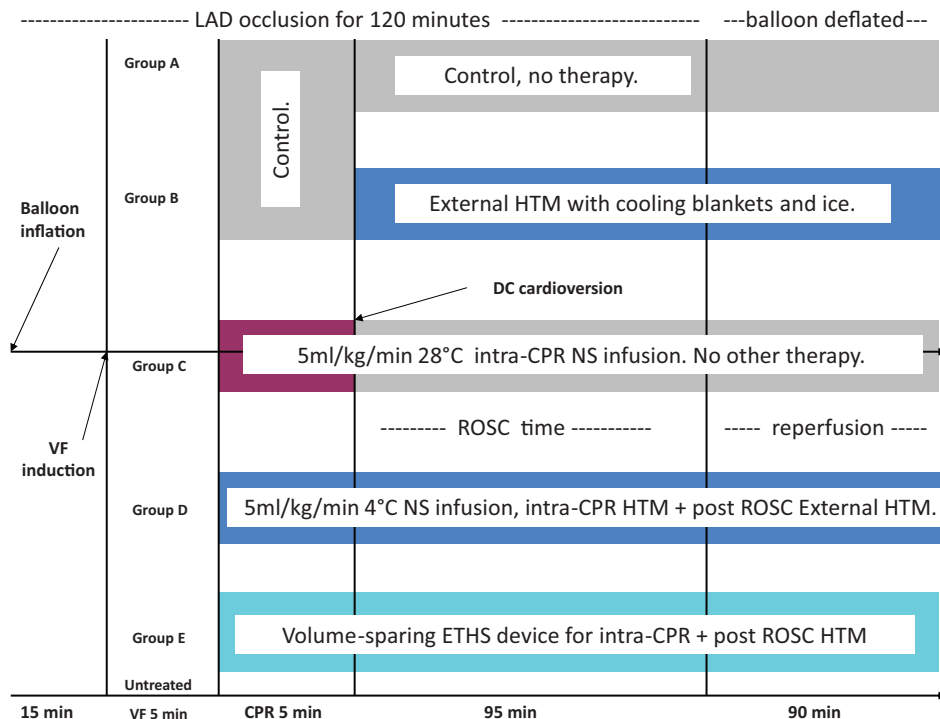
At minute 5 of CPR, 0.8 mg epinephrine was given intravenously, and the first 150-J biphasic DC shock was delivered 30 seconds later with continuation of the compressions until a separate pressure waveform was seen on the aortic pressure waveforms or until 2 minutes had passed, at which point brief discontinuation of compressions allowed assessment of rhythm and pressure check. Advanced cardiac life support guidelines were followed for up to 20 minutes in all animals before efforts were stopped.

In the animals that had ROSC, ventilation rate was adjusted to 14 to 18 breaths per minute on the basis of  $\text{ETCO}_2$  and blood gas values. In addition, anesthesia was reinitiated. Mean arterial pressure was maintained  $>50$  mm Hg with epinephrine boluses of 0.2 to 0.5 mg. All animals also received pancuronium bromide 0.1 mg/kg IV repeated as needed to prevent shivering and muscle movement. Cardiopulmonary resuscitation and cardioversion shocks were delivered as needed if ventricular fibrillation, pulseless electrical activity, or asystole recurred at any point.

Balloon inflation was maintained for a total of 120 minutes. At minute 120, the balloon was deflated but left in place, and flow to the distal LAD was documented with a small 5-cm<sup>3</sup> contrast injection. Reperfusion was maintained for another 90 minutes. Subsequently, the aortic pigtail was removed, and a pediatric JR2 diagnostic catheter was used to engage the right coronary artery.

### Determination of Area at Risk and Infarction Size

After engagement of the right coronary artery, the LAD balloon was reinflated at the previous position and confirmed by the screen marking at the same projection. After verification of the correct position, 20 mL of 2,3,5-triphenyltetrazolium chloride (TTC) was infused through the balloon lumen. While the LAD balloon was still inflated, 30 and 50 cm<sup>3</sup> of 1% Evans Blue were infused in the right coronary artery and left main arteries through the JR2 and SAL 0.75 catheters, respectively. The combination of the infusion of those 2 dyes was lethal by developing asystole after severe widening of the QRS within 1 to 2 minutes. Subsequently, the hearts were excised



**Figure 1.** Schematic of the experimental protocol. HTM indicates hypothermia; NS, normal saline; and VF, ventricular fibrillation.

and sliced into 10-mm slices parallel to the atrioventricular groove from the apex to the base. The slices were then submerged into 37°C 1% TTC solution and left to incubate for 20 minutes. All slices were then weighed and photographed over a white background with a ruler marking. Infarction size and ratio of the infarction to myocardial risk area were calculated using standard methods.<sup>24</sup>

### Group Interventions

The 46 animals were prospectively randomized to 5 groups.

#### Group A (n=9)

This was the no-intervention control group. Fifteen minutes of LAD occlusion was followed by 5 minutes of untreated ventricular fibrillation and then 5 minutes of vest CPR. In the animals that survived, the balloon was deflated after 120 minutes of LAD occlusion. Reperfusion lasted for 90 minutes, at which point the experiment was terminated with intracoronary infusion of Evans Blue and TTC as described above.

#### Group B (n=9)

The first 25-minute segment of the experiment was identical to group A. After ROSC and as soon as circulation was stabilized (mean time to application,  $12 \pm 5$  minutes after first ROSC), external hypothermia was applied with a Gaymar MTA6900 Medi-Therm III Hyper/Hypothermia System using external cooling blankets and surface cooling with ice water-soaked towels. Hypothermia target was set to 32°C to 33°C measured at the transverse sinus (intracranial thermocouple) and if achieved was continued for the duration of the experiment.

#### Group A+B for CPR

Animals included in the first 2 groups (18 animals) served as the control group for CPR because they received identical therapy during CPR. They are referred to as group A+B.

#### Group C (n=8)

Group C is similar to group A with the exception of intra-CPR infusion of 5 mL · kg<sup>-1</sup> · min<sup>-1</sup> of 28°C (room temperature) normal saline 0.9% starting at the same time as the initiation of chest compressions. There was no other intervention after ROSC.

#### Group D (n=11)

Intra-CPR infusion of 4°C normal saline 0.9% at 5 mL · kg<sup>-1</sup> · min<sup>-1</sup>, which was started at the same time as chest compressions, was followed by post-ROSC external hypothermia as in group B for the duration of the experiment.

#### Group E (n=9)

The intravascular hypothermia device was turned on with CPR initiation and automatically controlled target temperature until the end of the study. The device was removed just before the right coronary artery catheter was inserted for the dye injections. Graphic presentation of the different group treatments is shown in Figure 1.

### Definitions

Coronary perfusion pressure was calculated as diastolic aortic pressure minus diastolic right atrial pressure during CPR and as diastolic aortic pressure minus LVEDP after successful resuscitation. Target temperature was defined as transverse sinus temperature of 32°C to 33°C. Temperature homeostasis was defined when equilibration of all 3 vascular temperatures ( $\leq 33 \pm 0.5^\circ\text{C}$ ) was achieved and all 3 were within 1°C of the tympanic temperature. Myocardial infarction end points were expressed as percent infarction to LV weight and as percent infarction to myocardium area at risk (AAR) weight.

### Statistical Analysis

Values are expressed as mean  $\pm$  SD. We used MedCalc and Origin (version 7.5) data analysis software programs. The primary end point was the percent infarction to AAR. ROSC, total dose of epinephrine, number of shocks delivered, total minutes of CPR, and episodes of recurrent cardiac arrest were secondary end points. A single-factor ANOVA was used to determine statistical significance of differences in means of continuous variables between groups. Pairwise comparison of subgroups was performed with the Student-Newman-Keuls test. A Boltzmann regression analysis was used between percent infarction to AAR and time to reach target temperature. Significance was set at a value of  $P < 0.05$ . A 2-tailed Fischer exact test was used for ROSC rates and pulseless electrical activity evaluation comparisons. The numbers of the animals in each group were allocated by

**Table 1. Different Hemodynamic Parameters of All 5 Groups at Baseline, During CPR, and at 60 and 120 Minutes After ROSC**

	Group A	Group B	Group C	Group D	Group E
Baseline					
MAP, mm Hg	99.5±11	92.6±10.7	93.8±12	92.1±7	96.5±12
CPP, mm Hg	76.3±8	70±10	71±10	71±8	73.9±13
RAP, mm Hg	9.6±3	8.2±3	8.6±4	11±2	7.9±3
LVEF, %	68±4	66±3.6	65±5	66±4.5	62±3
LVEDP, mm Hg	9.6±2.6	11±3	11.3±4	7.7±5	10.5±3
CPR					
SBP, mm Hg	99.8±22	99±26	102±18	111±17	113±29
DBP, mm Hg	36.6±8	37.9±8	33±7	37.6±6	32.3±15
CPP, mm Hg	20.6±8†‡	20.1±8†‡	12.8±5	14.6±10	21.3±12†‡
RAP, mm Hg	16±3.8†‡	17.8±6.4†‡	26±8.8*	25.4±5.8*	12±5.7
At 60 min after ROSC					
MAP, mm Hg	91.5±10	81.5±13	78	76.3±10.3	90.3±21.5
CPP, mm Hg	67.2±10†	57.±15	33	54.5±8	67.3±21†
RAP, mm Hg	13±7	14.8±8	22	16.5±4*	10.5±4
LVEF, %	22.6±4*†	21±2.5*†	18	17.7±2*	32.5±4
LVEDP, mm Hg	22.4±3*†	23.8±3*†	32	28.5±5*	15.6±4.7
At 120 min after ROSC					
MAP, mm Hg	82.5±11	82.8±15	66	72.2±11	76.4±21
CPP, mm Hg	48±7	52±6	38	49.9±10	54.8±19
RAP, mm Hg	13.6±5	14.8±2	21	19.1±4*	9.9±4
LVEDP, mm Hg	21.8±3*†	24.8±6*	29	28.5±4*	13.7±2

MAP indicates mean arterial pressure; CPP, coronary perfusion pressure; RAP, right atrial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; and LVEF, LV ejection fraction. Values are mean±SD.

\*Statistically significant difference ( $P<0.05$ ) vs group E (ETHS device, volume sparing, hypothermia).

†Statistically significant difference vs group D (4°C saline infusion intra-CPR hypothermia followed by post-ROSC external hypothermia).

‡Statistically significant difference vs group C (intra-CPR room-temperature intravenous saline infusion).

the randomization process prospectively. The pooling and analysis of the data of different groups were planned prospectively.

**Results**

Baseline hemodynamic parameters were similar in all 5 groups, as shown in Table 1. Blood gasses and ETco<sub>2</sub> were not statistically different between all animal groups.

**Resuscitation Rates**

ROSC was significantly improved in the ETHS device, volume-sparing, hypothermia group (group E) compared with groups C, D, and A+B (100% versus 12.5%, 54%, and 55%;  $P<0.05$ ). In addition, room-temperature volume loading (group C) significantly decreased ROSC rates compared with group A+B ( $P<0.05$ ; Table 2).

**Resuscitation Parameters**

As Table 2 shows, the no-volume ETHS device intra-CPR hypothermia group (group E) had a significant advantage in all the measured resuscitation parameters, with fewer number of shocks to the first ROSC, fewer total shocks and doses of epinephrine, smaller total dose of epinephrine, fewer total minutes of CPR, and fewer animals that developed pulseless electrical activity. On the other hand, cold saline infusion during CPR (group D) offered no advantage over controls.

Room-temperature intra-CPR fluid infusion (group C) adversely affected ROSC rates and all the resuscitation parameters.

**Myocardial Infarction and LV Function**

Figure 2 shows representative pathology specimens from the different groups. There were no significant differences in the AAR between groups (Figure 3A). The percent infarction to LV weight and percent infarction to AAR were significantly reduced with intra-CPR application of hypothermia (groups D and E) compared with the other groups. Use of the volume-sparing ETHS device for intra-CPR hypothermia (group E) further reduced infarction size and percent infarction to AAR compared with cold saline infusion during CPR followed by post-ROSC external hypothermia (group D; Figure 3B, 3C, and 3D).

The times to reach target temperature (32°C to 33°C) and temperature homeostasis were significantly faster in the ETHS intra-CPR hypothermia group (group E) compared with both groups D and B (Table 2). Three real-time vascular and tympanic temperature recordings from animals in groups B, D, and E are shown in Figure 4. Animals in group C (28°C saline infusion) had no clinically significant changes in transverse sinus and aortic temperatures during the experi-



**Table 2. Different Resuscitation Parameters in the 5 Groups**

Resuscitation Parameters	Group A	Group B	Group C	Group D	Group E
Shocks to ROSC, n	2.6±1.2	3.3±1*†	6	2.3±0.9	2.3±1.5
Total shocks, n	3.5±1.2	4.8±0.8	9	3.7±1.7	3.4±3.1
Epinephrine doses to ROSC, n	2.5±1.1*†	2.3±0.5*†	4	4.5±1*	1.4±0.7
Post-ROSC epinephrine doses, n	4.3±3*	2.3±2*	3	4.3±3*	1.2±1.2
Total epinephrine, mg	4.9±2.4*	3.9±1.8*†	4.5	6.4±2.5*	2.9±2.4
Total CPR in survivors, min	5.2±0.4†	8.3±3*	12	9.6±3.5*	5.4±0.7
Pulseless electrical activity, n	4/9+6/9=10/18*		8/8*	9/11*	1/9
Recurrent CPR, n	0.7±1.2	1.3±0.5	2	2±0.6	0.3±0.5
ROSC, n	6/9+4/9=10/18*‡		1/8*	6/11*	9/9
Time to target temperature, min	NA	190±76*†	NA	80±14*	16.6±7
Time to temperature homeostasis, min	NA	NA	NA	112±27*	31±11

Values are mean±SD.

\*Statistically significant difference ( $P<0.05$ ) vs group E (device, volume sparing, hypothermia).

†Statistically significant difference vs group D (4°C saline infusion intra-CPR hypothermia followed by post-ROSC external hypothermia).

‡Statistically significant difference vs group C (intra-CPR room-temperature intravenous saline infusion).

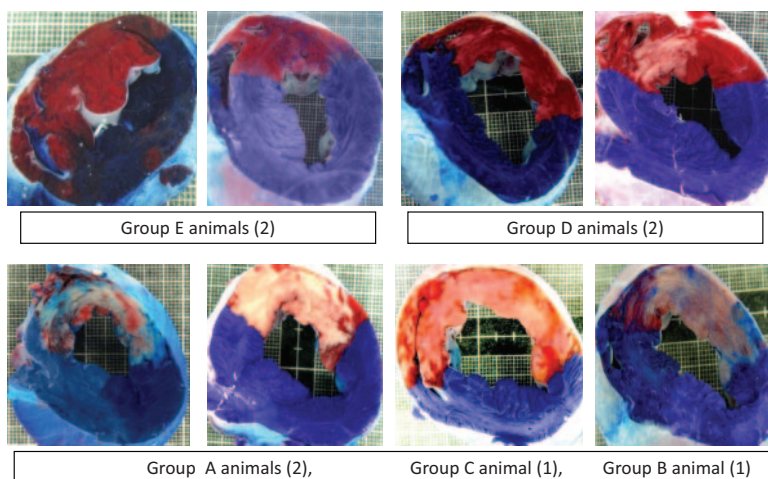
ment. Animals with only post-ROSC external hypothermia (group B) never reached temperature homeostasis in the duration of the experiment and reached target temperature after reperfusion (Table 2). The time to reach target temperature was directly related to the percent infarction to AAR and showed a sigmoid correlative association with a  $R^2=0.95$  and  $P<0.001$ . As Figure 5 shows, the percent infarction to AAR was significantly decreased with the application of intra-CPR hypothermia with and without volume infusion. Animals that did not receive intra-CPR hypothermia (groups A, B, and C) had no significant differences in infarction size, and external surface hypothermia did not protect against evolution of myonecrosis, although 5 animals achieved target temperature an average of  $134\pm11$  minutes after LAD occlusion.

One hour after ROSC, LV function was significantly better in the ETHS device, volume-sparing, hypothermia group (group E) compared with all other groups (Table 1). Animals in the control (group A) and external, surface-only, hypothermia (group B) groups had significantly better post-ROSC LV

function compared with the 4°C saline infusion intra-CPR hypothermia group (group D), suggesting that volume infusion significantly impaired LV function after ROSC. In addition, animals in groups C and D that received intra-CPR volume infusion had significantly elevated LVEDP compared with the other groups (Table 1). Pulmonary edema was documented in only 4 animals: 3 animals in group D and 1 animal in group C. All episodes were successfully treated with a 40-mg intravenous furosemide injection.

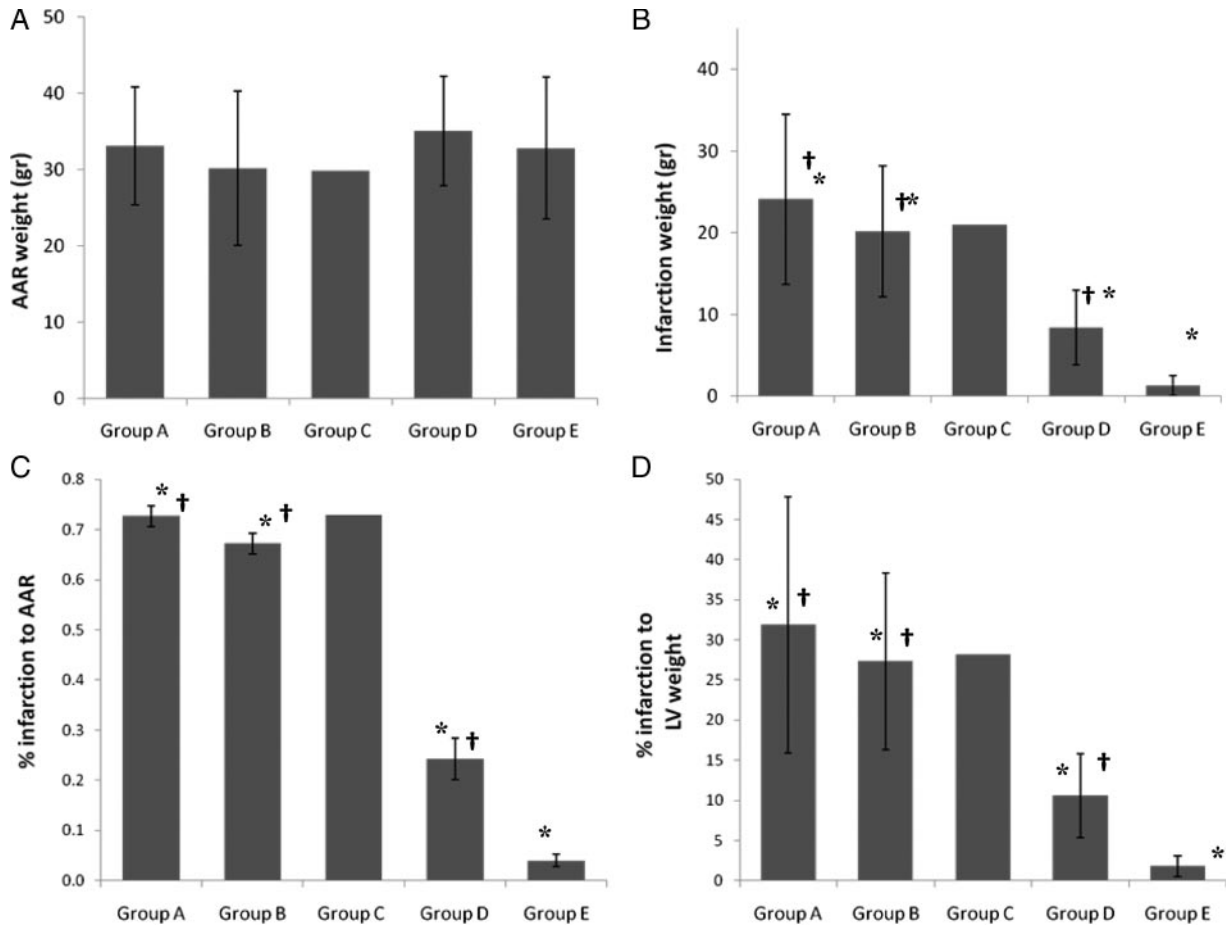
## Discussion

Early intra-CPR application of mild to moderate hypothermia has been shown to improve neurological outcomes in different animal models of cardiac arrest even when ROSC was delayed until mild hypothermia target was achieved.<sup>16,17</sup> Our study was designed to assess the effects of early intra-CPR application of mild to moderate hypothermia in an ischemic model of cardiac arrest with and without volume loading. The first significant finding of this investigation was that intra-CPR hypothermia has the potential to decrease myocardial



**Figure 2.** Real photographs of midcavity LV slices. The numbers in the parentheses represent the numbers of animals depicted. Blue stain (Evans Blue) represents healthy myocardium. Red myocardium (TTC stained) represents noninfarcted myocardium inside the AAR. White myocardium represents myonecrosis with absence of TTC staining inside the AAR. White and red areas represent the total AAR.

Blue: normal LV area; Red: viable area at risk; White: infarction area; Red + White = area at risk.



**Figure 3.** Infarction and AAR data (mean±SD) of all 5 groups. \*Statistically significant difference ( $P<0.05$ ) vs group E (ETHS device, volume-sparing, hypothermia); †statistically significant difference vs group D (4°C saline infusion intra-CPR hypothermia followed by post-ROSC external hypothermia).

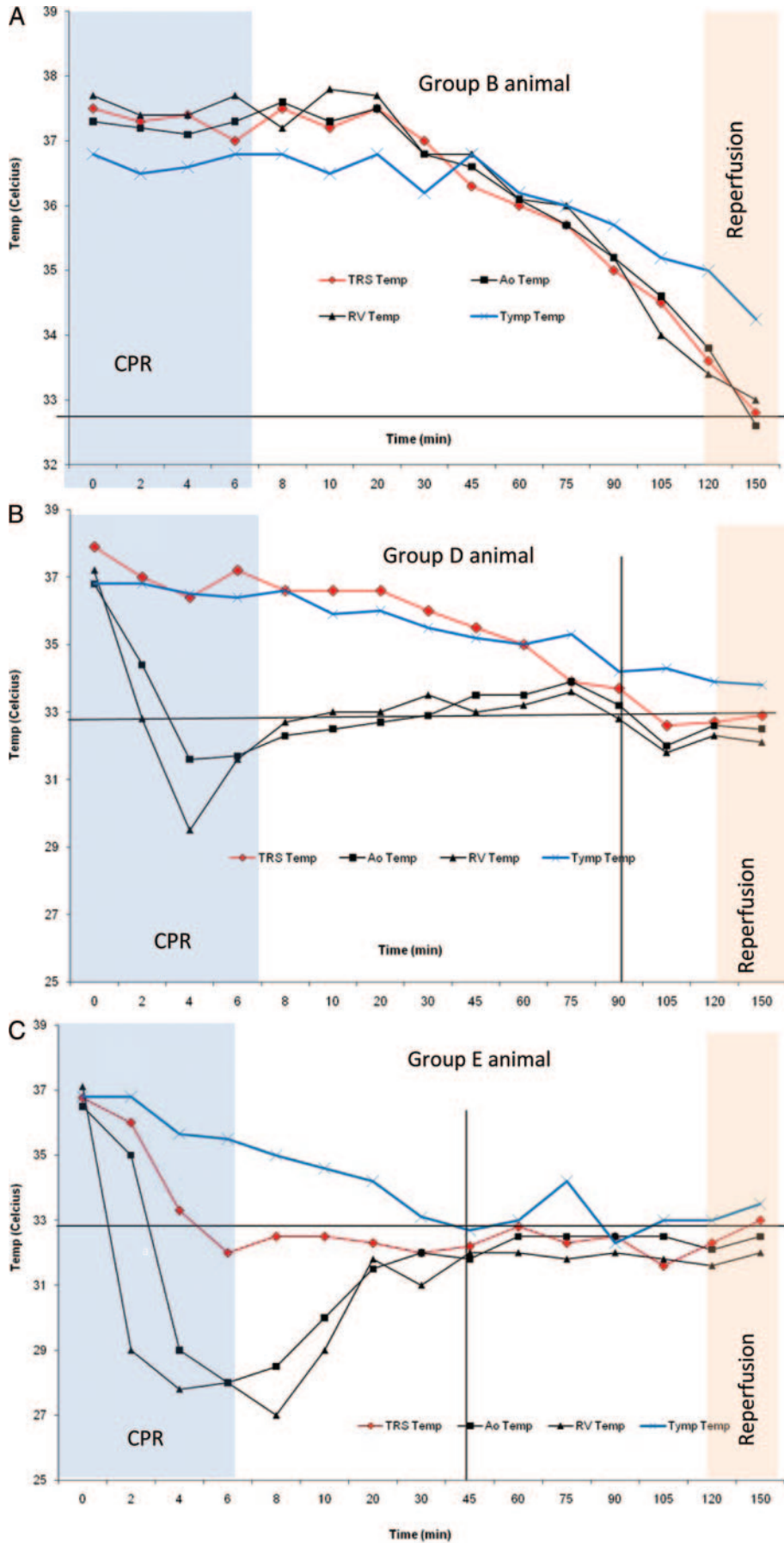
infarction size in this porcine model of cardiac arrest with ischemia and reperfusion. Although the observation of myocardial protection during ST-elevation myocardial infarction with hypothermia has been previously described and appears to be time dependent, patients with cardiac arrest, a group with a high prevalence of occlusive coronary artery disease,<sup>4</sup> can be very quickly identified and targeted for early intra-CPR hypothermia therapy.

The second important finding was that intra-CPR hypothermia without volume loading had significant advantage in resuscitability. The observation that normothermic volume loading in group C resulted in detrimental loss of coronary perfusion pressure and severely impaired resuscitation rates, combined with the improved ROSC rates despite poor coronary perfusion in the cold saline infusion, proves that the benefit in myocardial infarction size observed in group D was not due to volume loading but rather to the protection offered by hypothermia. This observation is consistent with the findings of Ditchy et al,<sup>25</sup> who investigated the effects of volume loading during CPR and found that although forward cardiac flow increases, cardiac blood flow and cerebral blood flow decrease significantly, mainly as a result of an increase in right atrial pressure. From these findings, it is obvious that to maximize intra-CPR hypothermia protection, a volume-

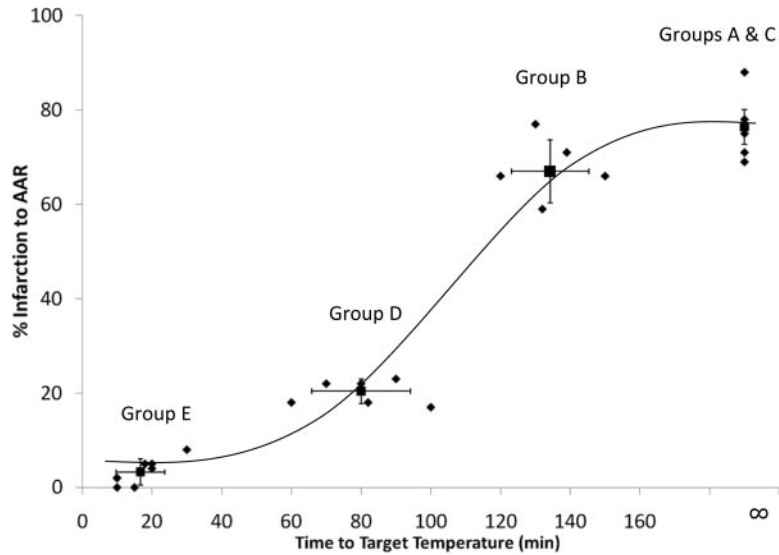
sparing, highly efficient, and easily deployed strategy or device is needed.

An interesting question-generating observation was that the myocardial protection benefit of hypothermia was not associated with the time of application of hypothermia but with the efficiency of the method to reach target temperature and apparently temperature homeostasis. The animals that had surface external hypothermia application reached target after reperfusion, which resulted in the absence of protection against infarction development. In contrast, the animals that received early hypothermia starting during CPR and then reached target temperature before reperfusion had smaller infarctions, and the consistency of their infarctions was patchier with islands of infarction within areas of healthy myocardial cells. These data are in concordance with previously published animal experiments on the timing of hypothermia relative to reperfusion and validate our findings.<sup>7-11,26</sup>

In an effort to facilitate hypothermia as early as possible, Kim et al<sup>27</sup> introduced cold saline infusion immediately after ROSC in survivors of cardiac arrest. Our study investigated the effects of the earliest possible application of cold saline infusion, which is at the initiation of CPR. Volume loading in group D resulted in a significantly decreased post-ROSC ejection fraction and significantly elevated LVEDP compared with all other groups. The use of epinephrine, the recurrence



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**Figure 5.** Sigmoid asymptotic fit showing the relation between the percent infarction to AAR and time to reach target temperature (transverse sinus temperature  $\leq 33^{\circ}\text{C}$ ) with  $r^2=0.95$ . This figure clearly shows that the sooner target temperature is reached, the larger the protective effect of hypothermia on infarction protection is. Reaching target temperature after reperfusion is of no benefit.

of cardiac arrest, and CPR were significantly higher compared with controls, suggesting that despite the improvement in infarct size, the post-ROSC cardiac global dysfunction is exacerbated by fluid loading. Unfortunately, the volume needed to effectively “jump start” the hypothermic effect on myocardial protection can by itself adversely influence post-resuscitation LV function and filling pressures, as our study has clearly shown. Obviously, that disadvantage must be compared with the cerebral and cardiac protection offered by such a therapeutic approach because postresuscitation volume loading and high filling pressures can be treated effectively with modern medical therapy (ie, diuretics and inotropes).

When hypothermia was introduced early without volume loading, the benefit was potentiated, as shown by the significant improvement in ROSC rates in group E and the lower LVEDP and higher coronary perfusion pressure in the post-resuscitation period of ischemia. The size of the infarction was limited further and led to a marked improvement in LV systolic function 60 minutes after ROSC. This finding is especially important if we consider that post-cardiac arrest systolic dysfunction is a significant predictor of short-term survival.<sup>28</sup> The global improvement of function can be contributed to many factors such as lower total dose of epinephrine, fewer shocks, smaller infarction size, and lower LVEDP and cannot solely be attributed directly to hypothermia. Hypothermia has been shown to increase cardiac contractility, to decrease diastolic compliance, and to decrease heart rate and oxygen uptake in isolated heart preparations and failing human hearts.<sup>29,30</sup> In general, hypothermia typically delays contraction kinetics so that the duration of systole gets prolonged and impairs relaxation.<sup>31,32</sup> The mech-

anism of global protection and improvement of contractility remains hypothetical.

The clear association between the time to target temperature ( $32^{\circ}\text{C}$  to  $33^{\circ}\text{C}$ ) and myocardial infarction size has provided insights into the window of opportunity for therapeutic hypothermia. It appears that even when the ischemic time is short before the application of hypothermia (total of 20 minutes), target temperature needs to be reached within 1 hour (60 minutes) and definitely before 2 hours (120 minutes) because after that time period it appears that there is no benefit (as can be seen in group B) compared with controls. The association appears to be best described with a sigmoid curve, with the lower asymptotic being close to 6% and the upper asymptotic being  $>70\%$  of infarction-to-AAR ratio. The upper limit is defined by the preformed collateral density and collateral recruitment time for each species. In humans, because the preformed collateral density is different, the upper asymptotic should also be different and probably lower.<sup>33</sup> In addition, in patients with preexisting coronary artery stenoses and preformed collaterals, the benefit would be even further attenuated because the AAR from an acute occlusion is significantly limited by the presence of collateral flow.<sup>34</sup>

In group E, hypothermia was induced very quickly, and the target temperature with vascular temperature equilibrium was achieved faster than in any other group. The intravenous balloon catheter was used to investigate the maximum effect that can be achieved by a very effective cooling method, although the clinical relevance is unclear because of the complexity of the introduction of the catheter. The benefits observed in group E strongly suggest that efforts should be

**Figure 4 (Continued).** A, B, and C, Real-time temperature recordings from animals in group B (post-ROSC external hypothermia only), group D ( $4^{\circ}\text{C}$  saline infusion intra-CPR hypothermia followed by post ROSC external hypothermia), and group E (device, volume-sparing, hypothermia). Horizontal line shows target temperature; perpendicular line, time to reach temperature homeostasis. TRS indicates transverse sinus; Ao, aortic; Tymp, tympanic; and RV, right ventricular temperatures.



made to develop an effective hypothermic, volume-sparing device that can be easily deployed.

This study used a porcine model of ischemic cardiac arrest. The majority of CPR or resuscitation experiments in animals are performed in intact hearts with open arteries. This model offers a more realistic simulation of human cardiac arrest resuscitation because most of the events are ischemic. The poor resuscitation rates observed in this experiment with shorter untreated ventricular fibrillation and CPR times than our previous work<sup>23,35,36</sup> can be explained by the severity of the model and the significant postresuscitation instability derived from the ischemic and very arrhythmogenic substrate in this animal model.<sup>37,38</sup>

Our study has several limitations. It is not possible to say whether the effect of hypothermia on myocardial ischemic injury was due to the timing of or to differences in myocardial temperatures achieved during the experiments with different methods of hypothermia induction. It is very likely that directionality of cooling (external versus internal) and its direct contact effects with the perfused organs may be very important in this process and need further investigation.

We did not test the application of the intravascular hypothermia system and cold volume loading after resuscitation because that was not our hypothesis-derived question. Our efforts were aimed at answering the question, does intra-CPR hypothermia improve resuscitation rates and decrease infarct size compared with the therapy and postresuscitation external cooling that are currently the standard of practice? In our study, it was clear that intra-CPR hypothermia without volume loading offered an advantage for resuscitation compared with all other groups.

We cannot exclude that the pathology staining results could have been influenced by tissue temperature at the end of the study. The protocol dictated that there would be temperature differences in different groups at the end of the reperfusion period. If there is a temperature effect on tissue staining, then we could have overestimated the benefits observed. We are unaware of such an interaction. In addition to smaller infarction size, group E had lower LVEDP and better LV function, a finding that supports the histology data.

### Conclusions

Intra-CPR hypothermia significantly decreased infarction size in this ischemic model of cardiac arrest and resuscitation. Intra-CPR volume loading adversely affects resuscitation rates, post-ROSC management, and LV function. The biggest benefit, including the combination of improved resuscitation rates, post-ROSC LV function, and infarction limitation, is observed with volume-sparing, intra-CPR hypothermia and quick target temperature achievement. Further research is warranted to evaluate methods and technologies that can be easily deployed in the field and can cool quickly and reliably.

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### Disclosures

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### CLINICAL PERSPECTIVE

Therapeutic hypothermia has been shown to improve neurological outcomes in humans when applied in comatose victims of cardiac arrest. In animal studies, intra-cardiopulmonary resuscitation application of hypothermia further improves neurologically intact survival. Most of the out-of-hospital cardiac arrests are due to ischemic complications of coronary artery disease. We investigated the effects of intra-cardiopulmonary resuscitation hypothermia with and without volume loading on resuscitation rates and infarction size in a porcine ischemia/reperfusion model (left anterior descending artery occlusion) of cardiac arrest and resuscitation. The findings of this study suggest that intra-cardiopulmonary resuscitation hypothermia can limit the size of myocardial infarction and improve postresuscitation cardiac function. Compared with hypothermia achieved with infusion of cold saline, application of hypothermia with an intravascular device without volume loading improved resuscitation rates and postresuscitation LV function and further limited the size of myocardial infarction. It also appears that faster cooling improves protection against myocardial infarction. An intravascular device that can be readily deployed in the field does not currently exist. On the basis of this study, methods to achieve fast and effective hypothermia without volume loading should improve the effect of early application of this therapy during cardiopulmonary resuscitation and warrant further investigation.

## Intra-Cardiopulmonary Resuscitation Hypothermia With and Without Volume Loading in an Ischemic Model of Cardiac Arrest

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