JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 23, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.08.040

Importance of Both Early Reperfusion and Therapeutic Hypothermia in Limiting Myocardial Infarct Size Post–Cardiac Arrest in a Porcine Model

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CME Objective for This Article: At the end of the activity the reader should be able to: 1) appreciate the synergistic effect of combined therapeutic hypothermia and early reperfusion in reducing infarct size; 2) recognize the time discordance in clinical manifestations between large experimental models and the clinical setting; and 3) consider differences in infarct size between treatment groups of hypothermia and reperfusion versus no hypothermia and reperfusion versus hypothermia and no reperfusion.

CME Editor Disclosure: *JACC: Cardiovascular Interventions* CME Editor Bill Gogas, MD, PhD, has reported that he has no disclosures.

Author Disclosures: This work was funded by the Steven M. Gootter Foundation and Zoll Circulation. Dr. Kern is a member of the science advisory board for Zoll Medical. Dr. Illindala was an employee of Zoll Circulation during this study. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

Issue Date: December 12, 2016
Expiration Date: December 11, 2017

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Manuscript received July 13, 2016; revised manuscript received August 23, 2016, accepted August 25, 2016.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 23, 2016
DECEMBER 12, 2016:2403–12

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ABSTRACT

OBJECTIVES The aim of this study was to test the hypothesis that hypothermia and early reperfusion are synergistic for limiting infarct size when an acutely occluded coronary is associated with cardiac arrest.

BACKGROUND Cohort studies have shown that 1 in 4 post-cardiac arrest patients without ST-segment elevation has an acutely occluded coronary artery. However, many interventional cardiologists remain unconvinced that immediate coronary angiography is needed in these patients.

METHODS Thirty-two swine (mean weight 35 ± 5 kg) were randomly assigned to 1 of the following 4 treatment groups: group A, hypothermia and reperfusion; group B, hypothermia and no reperfusion; group C, no hypothermia and reperfusion; and group D, no hypothermia and no reperfusion. The left anterior descending coronary artery was occluded with an intracoronary balloon, and ventricular fibrillation was electrically induced. Cardiopulmonary resuscitation was begun after 4 min of cardiac arrest. Defibrillation was attempted after 2 min of cardiopulmonary resuscitation. Resuscitated animals randomized to hypothermia were rapidly cooled to 34°C, whereas those randomized to reperfusion had such after 45 min of left anterior descending coronary artery occlusion.

RESULTS At 4 h, myocardial infarct size was calculated. Group A had the smallest infarct size at 16.1 ± 19.6% ($p < 0.05$). Group C had an intermediate infarct size at 29.5 ± 20.2%, whereas groups B and D had the largest infarct sizes at 41.5 ± 15.5% and 41.1 ± 15.0%, respectively.

CONCLUSIONS Acute coronary occlusion is often associated with cardiac arrest, so treatment of resuscitated patients should include early coronary angiography for potential emergent reperfusion, while providing hypothermia for both brain and myocardial protection. Providing only early hypothermia, while delaying coronary angiography, is not optimal. (J Am Coll Cardiol Intv 2016;9:2403–12) © 2016 by the American College of Cardiology Foundation.

An estimated 370,000 cardiac arrests will occur in the United States this year (1). Improvements in our initial treatment of such patients have resulted in an increasing number being successfully resuscitated and admitted to the hospital for further post-cardiac arrest care (2–8). The vast majority are comatose on arrival, making their long-term prognosis difficult to determine in the first few hours or days. In cohort population studies, aggressive post-resuscitation care including targeted temperature management (therapeutic hypothermia) and early coronary angiography has resulted in improved long-term survival rates of 50% to 60% among those whose initial cardiac arrest rhythm was ventricular fibrillation (VF) (9). Nearly 90% of such survivors achieve long-term, favorable neurological function (9,10).

Current European Society of Cardiology and the joint American College of Cardiology/American Heart Association guidelines post-cardiac arrest patients with ST-segment elevation strongly advise (class I recommendation) that all such patients, including those who remain unconscious, undergo immediate coronary angiography with the intent to reperfuse any acutely occluded culprit coronary artery (11,12). Unfortunately, recommendations for those post-cardiac arrest patients without ST-segment elevation are either lacking (12) or are much less emphatic (11).

Importantly, the 12-lead electrocardiogram post-cardiac arrest has proved unreliable in identifying acutely occluded culprit coronary arteries (13,14). In these resuscitated patients, the lack of ST-segment elevation does not rule out an acute coronary occlusion. Cohort studies have shown that approximately 1 in 4 post-cardiac arrest patients without ST-segment elevation has an acutely occluded coronary artery as the culprit for out-of-hospital cardiac arrest (15–18). Currently, many interventional cardiologists are unsure how to best approach these patients (19), with some favoring treatment with immediate targeted temperature management but delaying coronary angiography until evidence of favorable neurological recovery is seen.

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A relatively small experimental study has previously shown that hypothermia and early reperfusion are synergistic in limiting myocardial infarct size (20). Out-of-hospital cardiac arrest is often associated with an acutely occluded coronary artery. We hypothesized that all post-resuscitation patients should receive both therapeutic hypothermia and coronary angiography immediately upon arrival at the hospital. To examine this hypothesis, we performed a translational pre-clinical study using a porcine model of acute occlusion of the left anterior descending coronary artery (LAD) combined with VF cardiac arrest to evaluate the importance of simultaneously inducing therapeutic hypothermia and reperfusing an acutely occluded coronary in the early post-resuscitation period. The primary endpoint was myocardial infarct size.

METHODS

STUDY DESIGN. The study was conducted with the approval of the University of Arizona Institutional Animal Care and Use Committee. Each treatment group consisted of 8 domestic swine. After an induced acute anterior myocardial infarction (MI) and concurrent VF cardiac arrest, animals were randomly assigned to 1 of the following 4 treatment groups: group A, hypothermia with early reperfusion; group B, hypothermia with no reperfusion; group C, no hypothermia with early reperfusion; or group D, no hypothermia with no reperfusion.

ANIMAL PREPARATION. Anesthesia was induced using isoflurane inhalation (1% to 4%) administered by face mask. Ketoprofen or carprofen was administered for analgesia. Once a plane of anesthesia was reached to allow no jaw tone, an endotracheal tube was placed per os, and isoflurane was reduced to an appropriate level to maintain sedation.

Animals were placed on the table in dorsal recumbancy on a nonmetallic v-tray in the fluoroscopy suite. A rate- and volume-regulated ventilator (Narkomed 2A, North American Dräger, Houston, Texas) was used to maintain partial pressure end-tidal carbon dioxide at 40 ± 3 mm Hg, measured by mainstream infrared capnography (model 47210A, Hewlett-Packard, Palo Alto, California). Respiratory minute ventilation was measured using a pneumotachograph (Series 3850A; Hans Rudolph, Shawnee, Kansas). Electrocardiographic leads were attached to the animal to monitor cardiac rhythm. Using sterile technique, a surgical cut-down was performed for placement of introducer sheaths in the carotid artery and both the internal and external jugular veins. Percutaneous access was used for placement of sheaths in the femoral artery and vein. Once all applicable vessels were cannulated, heparin was administered to prevent clotting.

Solid-state pressure micromanometer catheters was placed in the right atrium and descending aorta for measuring pressures (right atrial pressure, aortic pressure). A Swan-Ganz catheter was placed in the pulmonary artery to measure pulmonary arterial pressure, pulmonary capillary wedge pressure, and thermodilution cardiac output. Baseline hemodynamic variables were recorded after a stabilization period following instrumentation of the animal.

MEASUREMENTS. Continuous measurements of right atrial pressure, aortic pressure, pulmonary arterial pressure, core temperature, electrocardiogram, partial pressure end-tidal carbon dioxide, and minute ventilation were recorded using data acquisition software (Lab Chart 8, AD Instruments, Sydney, Australia). Coronary artery perfusion pressure was calculated as mid-diastolic aortic pressure minus mid-diastolic right atrial pressure and also as the integrated area between the aortic and right atrial diastolic pressure curves. Arterial blood samples were drawn at baseline for blood gas analyses. Cardiac output was measured at baseline and 1, 2, and 4 h post-occlusion, and a contrast left ventriculogram

ABBREVIATIONS AND ACRONYMS

LAD = left anterior descending coronary artery

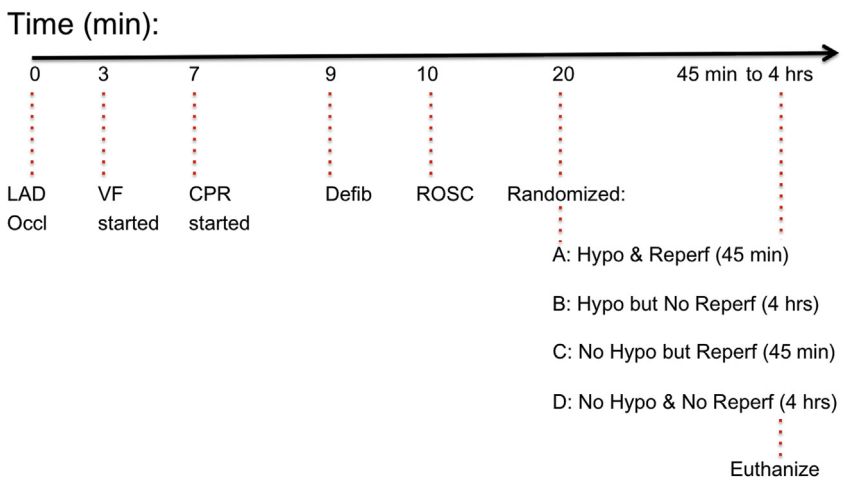
MI = myocardial infarction

VF = ventricular fibrillation

TABLE 1 Four Different Study Groups

	Group A	Group B	Group C	Group D
Cooling	Immediate	Immediate	None	None
Goal	34°C	34°C	37°C–38°C	37°C–38°C
Reperfusion	Immediate	None	Immediate	None
Time	45 min	4 h	45 min	4 h

FIGURE 1 Study Protocol Timeline

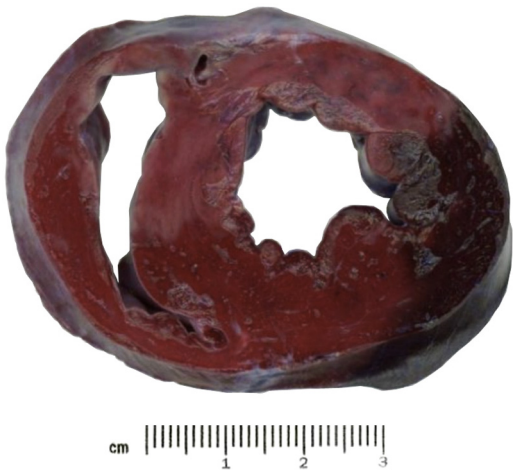


CPR = cardiopulmonary resuscitation; Defib = defibrillation; Hypo = hypothermia; LAD = left anterior descending coronary artery; Occl = occluded; Reperf = reperfusion of the occluded coronary artery; ROSC = return of spontaneous circulation; VF = ventricular fibrillation.

(via pigtail catheter in the left ventricle) was obtained at baseline and 4 h post-LAD occlusion.

EXPERIMENTAL PROCEDURE. Coronary occlusion for induction of an acute MI. A standard 6-F coronary interventional guide catheter was placed in an arterial sheath and advanced to the LAD. A coronary guidewire was placed in the LAD with its tip extending to the distal aspect of the vessel. A standard angioplasty balloon was advanced over the guidewire to the midportion of the LAD (distal to the third diagonal). The balloon was inflated to 8 atm, and duration of occlusion was according to the study designated group (45 min or 4 h). Occlusion was verified by selective coronary angiography.

FIGURE 2 Myocardial Slice From Group D Showing a Significant Area of Infarction



Purplish myocardium is the area not at ischemic risk, **bright red** is the area at ischemic risk but not infarcted, and **pale pink** or **white** is the area of ischemic risk that is infarcted.

Induction of VF cardiac arrest and resuscitation. Three min after LAD occlusion was verified, VF was electrically induced. Animals were maintained in untreated VF for 4 min to mimic "no-flow time" before the arrival of emergency medical services. At 7 min post-occlusion, cardiopulmonary resuscitation efforts, including chest compressions and advanced cardiac life support, were started until successful restoration of spontaneous circulation occurred or until 15 min had elapsed. Cardiopulmonary resuscitation consisted of active ventilation (oxygen set to 2 l and frequency set to 12 rpm) and continuous chest compressions of 100 compressions per minute for 2 min. Following 2 min of continuous chest compressions, compressions were stopped, and the electrocardiogram was analyzed to check the cardiac rhythm. If the animal was in VF, a single biphasic shock of 150 J was delivered via external defibrillator paddles and 1 mg intravenous epinephrine was administered. If the animal had pulseless electric activity, intravenous epinephrine 1 mg was administered, but no shock was administered.

TABLE 2 Baseline Demographic and Resuscitation Characteristics

	All (N = 32)	Group A (n = 8)	Group B (n = 8)	Group C (n = 8)	Group D (n = 8)	p Value*	Tukey HSD†
Weight (kg)	34.2 ± 4.7	32.9 ± 3.8	35.8 ± 3.9	34.6 ± 6.6	33.5 ± 4.4	0.64	
Male	28.1	12.5	25.0	25.0	50.0	0.52	
Heart rate (beats/min)	113.0 ± 17.5	107.9 ± 21.0	119.0 ± 19.4	118.7 ± 13.1	106.6 ± 14.4	0.33	
AoS (mm Hg)	86.4 ± 11.5	82.6 ± 9.6	84.2 ± 12.5	93.8 ± 8.5	84.8 ± 13.2	0.20	
AoD (mm Hg)	59.5 ± 9.9	54.8 ± 7.1	57.4 ± 10.4	68.5 ± 6.8	57.2 ± 10.2	0.02	C > A
RAM (mm Hg)	5.5 ± 3.0	6.4 ± 2.9	5.5 ± 2.0	4.2 ± 2.2	5.9 ± 4.3	0.49	
Cardiac output (l/min)	3.0 ± 0.6	2.7 ± 0.3	3.2 ± 0.6	3.1 ± 0.7	2.9 ± 0.6	0.39	
$PetCO_2$ (mm Hg) (n = 31)	41.3 ± 2.4	41.0 ± 3.2	40.6 ± 1.5‡	42.6 ± 2.7	41.0 ± 1.7	0.35	
LVEF (%) (n = 31)	56.9 ± 8.7	58.5 ± 8.0	61.4 ± 7.3	53.9 ± 10.64	53.4 ± 8.0	0.21	
Temperature (°C)	38.0 ± 0.6	37.8 ± 0.6	38.1 ± 0.7	37.9 ± 0.8	38.1 ± 0.5	0.66	

Values are mean ± SD or %. *Derived from one-way analysis of variance or Fisher exact test. †When overall p value was <0.05, post hoc Tukey HSD test was performed to identify the significant pairwise comparisons. ‡n = 7.

AoD = aortic diastolic pressure; AoS = aortic systolic pressure; HSD = honestly significantly different; LVEF = left ventricular ejection fraction; $PetCO_2$ = end-tidal carbon dioxide partial pressure; RAM = right atrial mean pressure.

Cardiopulmonary resuscitation was resumed and the treatment and analysis 2-min cycle repeated. Epinephrine administration was repeated every 3 min. Upon successful return of spontaneous circulation, post-resuscitation treatment according to the randomized group assignment (A, B, C, or D) was started.

Table 1 shows the 4 groups and their respective randomized treatments. In groups A and B, cooling began immediately after return of spontaneous circulation using a commercial cooling catheter (Thermoguard XP; Zoll, San Jose, California) inserted into the inferior vena cava. The target temperature was 34°C and once reached was maintained throughout the 4-h study period. In groups C and D, normal body temperature was maintained at 37°C to 38°C with a standard heating blanket (model K 20; GRI Medical Products, Cave Creek, Arizona) until 4 h post-occlusion.

In groups A and C, early reperfusion was accomplished at approximately 45 min post-occlusion by deflating the intracoronary balloon and removing it from the animal to allow reperfusion. In groups B and D, no reperfusion was done, but rather the intracoronary balloon remained inflated throughout the 4-h study period. Hemodynamic status was captured at 1, 2, and 4 h post-occlusion (Figure 1).

Myocardial infarct size measurement. Following the 4-h assessment of hemodynamic status, amiodarone and/or lidocaine was given to prevent

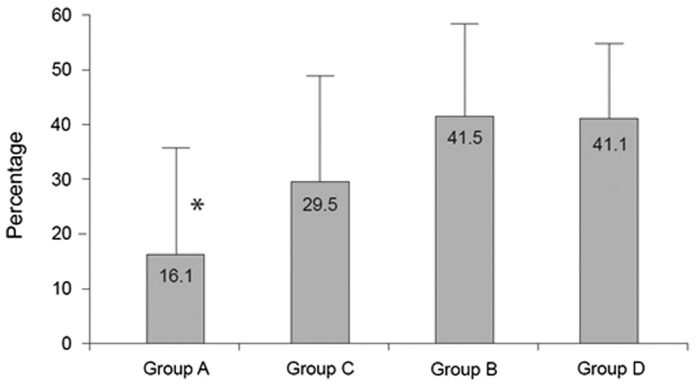
TABLE 3 Resuscitation Characteristics (After 1 Min of Cardiopulmonary Resuscitation)

	All (N = 32)	Group A (n = 8)	Group B (n = 8)	Group C (n = 8)	Group D (n = 8)	p Value*	Tukey HSD†
AoS (mm Hg)	130.5 ± 38.5	116.4 ± 20.5	139.7 ± 36.4	115.6 ± 47.5	150.1 ± 39.5	0.19	
AoD (mm Hg)	16.4 ± 10.2	16.5 ± 10.7	17.1 ± 12.0	17.9 ± 10.5	14.1 ± 9.0	0.90	
RAS (mm Hg)	226.9 ± 59.0	255.7 ± 56.8	207.9 ± 44.6	211.5 ± 78.4	232.5 ± 49.1	0.35	
RAD (mm Hg)	7.8 ± 3.0	8.0 ± 3.6	7.0 ± 2.2	8.6 ± 3.2	7.5 ± 3.4	0.78	
CPP (mm Hg)	8.6 ± 10.2	8.5 ± 7.8	10.1 ± 13.0	9.3 ± 10.2	6.6 ± 11.2	0.92	
$PetCO_2$ (mm Hg)	28.2 ± 4.5	26.8 ± 3.8	26.6 ± 5.3	29.3 ± 5.7	30.0 ± 2.2	0.33	
Time from occlusion to ROSC (min) (n = 30)	13.0 ± 4.8	11.3 ± 0.94	11.2 ± 1.14	14.5 ± 6.2	14.7 ± 6.4	0.31	
Time to 34°C (min) (n = 15)	54.4 ± 20.8	45.1 ± 19.6	65.2 ± 17.6‡	NA	NA	0.06	
Time of balloon deflation (45 min) (n = 16)	45.1 ± 4.0	44.2 ± 5.5	NA	46.0 ± 1.4	NA	0.39	
Time of balloon deflation (4 h) (n = 16)	240 ± 0.0	NA	240 ± 0.0	NA	240 ± 0.0		

Values are mean ± SD. *Derived from one-way analysis of variance or Fisher exact test. †When overall p value was <0.05, post hoc Tukey HSD test was performed to identify the significant pairwise comparisons. ‡n = 7.

CPP = coronary perfusion pressure; NA = not applicable; RAD = right atrial diastolic pressure; RAS = right atrial systolic pressure; ROSC = return of spontaneous circulation. other abbreviations as in Table 2.

FIGURE 3 Myocardial Infarct Size at 4 H



Bar graph showing the percentage of area at ischemic risk that was infarcted ±SD. Note that the order is A, C, B, and D on the x-axis. Group A, hypothermia and reperfusion; group C, no hypothermia and reperfusion; group B, hypothermia and no reperfusion; and group D, no hypothermia and no reperfusion. *p < 0.05 versus groups B and D.

recurrence of VF while reintroducing the guide catheter and guidewires. In groups A and C, the LAD was reinstrumented with a percutaneous coronary intervention balloon catheter placed at the previous intracoronary site. The balloon was reinflated and the vessel reoccluded. Coronary angiography was performed to verify the occlusion. A second catheter was placed in or near the right coronary artery. Ninety milliliters of Evans blue dye (60 ml in the LAD and 30 ml in the right coronary artery) was injected simultaneously into the coronary arteries. This delineated the myocardial "area at risk," which did not stain blue. In groups B and D, a catheter was placed in or near the right coronary artery. Each animal was then euthanized.

Euthanasia was performed using a commercial euthanasia solution (Fatal Plus [Vortech Pharmaceuticals, Dearborn, Michigan], 390 mg/ml, at 1 ml/lb body weight administered intravenously into the jugular vein). Death was confirmed via cessation of heart and lung sounds and flat-line on the electrocardiogram.

TABLE 4 Outcomes by Group

	Group A (n = 8)	Group B (n = 8)	Group C (n = 8)	Group D (n = 8)	p Value*	Tukey HSD†
Weight (kg)	32.9 ± 3.8	35.8 ± 3.9	34.6 ± 6.6	33.5 ± 4.4	0.64	
Total infarct size/entire AAR (%)	16.1 ± 19.6	41.5 ± 15.5	29.5 ± 20.2	41.1 ± 15.0	0.02	(B,D) > A
Total infarct size/total LV area (%)	5.2 ± 6.4	16.9 ± 4.6	11.8 ± 5.5	15.8 ± 8.8	0.01	(B,D) > A
Entire AAR/total LV area (%)	33.1 ± 16.1	45.6 ± 16.1	46.5 ± 20.7	39.4 ± 15.6	0.39	
Total LV area (cm^2)	47.1 ± 5.9	45.8 ± 6.3	45.8 ± 10.4	43.0 ± 8.3	0.76	
Total infarct size (cm^2)	2.3 ± 2.8	7.9 ± 3.0	5.5 ± 3.3	7.2 ± 5.3	0.03	B > A
Entire AAR (cm^2)	15.4 ± 7.0	21.3 ± 9.4	20.5 ± 7.3	17.4 ± 8.7	0.61	
Total healthy viable area (cm^2)	31.7 ± 9.1	24.5 ± 6.2	25.3 ± 12.6	25.5 ± 6.7	0.37	
Swan-Ganz temperature (BL) (°C)	37.8 ± 0.6	38.1 ± 0.7	37.9 ± 0.8	38.1 ± 0.5	0.66	
Swan-Ganz temperature (2 h) (°C)	34.1 ± 0.5	34.1 ± 0.5	37.8 ± 0.8	38.4 ± 0.9	<0.0001	(D,C) > (A,B)
Swan-Ganz temperature (4 h) (°C)	34.1 ± 0.6	34.1 ± 0.3	38.5 ± 0.8	39.6 ± 1.4	<0.0001	(D,C) > (A,B)
LVEF (BL) (%)	58.5 ± 8.0	61.4 ± 7.3	53.9 ± 10.6 (n = 7)	53.4 ± 8.0	0.21	
LVEF (4 h) (%)	45.9 ± 12.5	38.9 ± 16.2	38.3 ± 9.1 (n = 7)	35.3 ± 10.2	0.39	
LVEF (BL to 4 h) % difference	12.6 ± 10.5 p = 0.01‡	22.5 ± 15.5 p < 0.01	15.6 ± 12.4 (n = 7) p = 0.02	18.1 ± 8.2 p < 0.001	0.42	
AoS (BL) (mm Hg)	82.6 ± 9.6	84.2 ± 12.5	93.8 ± 8.5	84.8 ± 13.2	0.20	
AoS (4 h) (mm Hg)	79.3 ± 12.1	72.2 ± 8.1	84.3 ± 10.6	76.3 ± 12.8	0.19	
AoD (BL) (mm Hg)	54.8 ± 7.1	57.4 ± 10.4	68.5 ± 6.8	57.2 ± 10.2	0.02	C > A
AOD (4 h) (mm Hg)	50.7 ± 11.4	43.5 ± 12.4	56.0 ± 11.0	43.0 ± 11.0	0.09	
RAM (BL) (mm Hg)	6.4 ± 2.9	5.5 ± 2.0	4.2 ± 2.2	5.9 ± 4.3	0.49	
RAM (4 h) (mm Hg)	5.5 ± 2.5	5.7 ± 3.1	8.3 ± 3.9	8.7 ± 4.5	0.18	
Cardiac output (BL) (l/min)	2.7 ± 0.3	3.2 ± 0.6	3.1 ± 0.7	2.9 ± 0.6	0.39	
Cardiac output (4 h) (l/min)	2.3 ± 0.7	2.0 ± 0.5	2.9 ± 0.6	2.5 ± 0.6	0.04	C > B
Cardiac output (BL to 4 h) (l/min)	0.3 ± 0.6 p = 0.22	1.2 ± 0.8 p < 0.01	0.3 ± 0.5 p = 0.19	0.5 ± 0.8 p = 0.13	0.05	

Values are mean ± SD. *Derived from one-way analysis of variance. †When overall p value was <0.05, post hoc Tukey HSD test was performed to identify the significant pairwise comparisons. ‡Derived from paired Student *t* test for difference between BL and 4 h.

AAR = area at risk; BL = baseline; LV = left ventricular; other abbreviations as in Tables 2 and 3.

Tissue collection. Following euthanasia, a median sternotomy was performed to open the chest. Each heart was excised, cut into 10-mm-thick transverse slices, and then stained with tetrazolium chloride. This caused the myocardium to be stained 3 separate colors: area at ischemic risk stained deep red, infarcted tissue stained pale pink or white, and healthy tissue not at risk stained bluish purple (Figure 2). Each heart slice was then scanned digitally (Epson Perfection V600; Epson America, Long Beach, California) for subsequent analysis. The infarcted tissue was quantified using a software-based planimetric calculation (PictZar Pro; PictZar, Elmwood Park, New Jersey).

DATA ANALYSIS. For each categorical variable (e.g., sex), the frequency was reported. The Fisher exact test was performed to determine differences among the 4 groups. For each continuous variable, including myocardial infarct size (the primary endpoint), the mean ± SD were reported at baseline, during resuscitation, and 4 h post-resuscitation. One-way analysis of variance was performed to compare the means of each outcome and mean changes of each resuscitation characteristic from baseline to 4 h post-resuscitation among the 4 groups. For each 1-way analysis of variance, when inequality among the 4 groups was detected, a post hoc Tukey's honest significance test was performed to identify the significant pairwise comparisons. All statistical tests were 2-sided, with p values ≤0.05 considered to indicate statistical significance.

RESULTS

A total of 54 swine were used to obtain 32 prospectively randomized subjects (mean weight 36 ± 12 kg) that completed the full protocol. Twenty-two animals were excluded: 14 animals could not be resuscitated; 7 animals, though resuscitated, did not survive the 4-h study period; and 1 animal was excluded for technical issues due to inadequate administration of Evans blue dye to outline the myocardial area at risk.

Baseline characteristics are shown in Table 2. No significant differences were found, except that aortic diastolic pressure was higher in group C than group A. During the resuscitation effort, there were no significant differences among the groups (Table 3).

The primary outcome was myocardial infarct size, measured as the area of infarct/area at ischemic risk at 4 h. Significant differences were found among the 4 groups, with group A having the smallest infarct size at 16.1 ± 19.6% and group C an intermediate infarct size at 29.5 ± 20.2%. Groups B and D had the largest infarct sizes at 41.5 ± 15.5% and 41.1 ± 15.0%, respectively (Figure 3). There was no difference in myocardial infarct size between groups B and D. Similar results were found if infarct size was measured as the total infarct area/total left ventricular area (Table 4).

Left ventricular ejection fraction at 4 h varied from 45.9 ± 12.5% (group A) to 35.3 ± 10.2% (group D) but was not significantly different among the 4 groups. However, left ventricular ejection fraction at 4 h declined significantly from baseline in all 4 groups, with the largest decline seen in group B (Table 4).

Blood temperature, measured in the central circulation (pulmonary artery), was significantly lower at 4 h in groups A and B, as designated by the study protocol (Table 3).

Cardiac output in group B was significantly less than in group C at 4 h, and the change over time from pre-arrest baseline to 4 h post-resuscitation was also significant for group B (Table 4).

DISCUSSION

The common approach of providing immediate cooling but delaying coronary angiography and percutaneous coronary intervention for successfully resuscitated out-of-hospital cardiac arrest victims does not provide the optimal chance for limiting myocardial damage and infarct size. This preclinical, translational study suggests that such an approach is no better than when both cooling and reperfusion are delayed in a subject with an acute coronary occlusion. Cohort population studies of those without electrocardiographic evidence suggesting acutely occluded coronary arteries post-cardiac arrest have shown that at least 1 in every 4 such patients has an acutely occluded coronary (13–18). If immediate coronary angiography is not performed to find such occluded vessels, the chance to salvage myocardium is lost, and left ventricular function can be compromised. Providing only immediate therapeutic hypothermia cannot overcome the delay in reperfusion when angiography and potential percutaneous coronary intervention are not likewise performed immediately. Those subjects receiving both therapies early (group A) had a 61% decrease in MI size compared with those receiving neither treatment early (group D), as well as those receiving early hypothermia but not early reperfusion (group B).

Our study confirmed the finding of Dae et al. (20) that the combination of early hypothermia and early reperfusion (group A) decreased myocardial infarct size by 47% compared with normothermic reperfusion alone (group C).

The importance of early reperfusion on MI size is well accepted and at the foundation of the worldwide effort to achieve a <90-min "first medical contact to reperfusion" goal for all patients with ST-segment elevation MI undergoing primary percutaneous coronary intervention (21). Long-term survival has been directly correlated to this time continuum metric (22). The clinical evidence for the role of therapeutic hypothermia in limiting infarct size has been more difficult to establish. The clinical hypothermia trials in acute MI to date have been limited by small numbers of patients and thereby lacked significant power (23–28). However, recent pooled or combination analyses of the individual studies have shown consistent clinical benefits of limiting MI size and decreasing the development of heart failure (29,30).

The value of therapeutic hypothermia in resuscitated out-of-hospital cardiac arrest patients has been shown in 2 randomized controlled trials (31,32). Both survival and favorable neurological function was significantly better in out-of-hospital cardiac arrest patients treated with hypothermia than those who were not. Targeted temperature management has become a mainstay of post-resuscitation care. The benefit of mild therapeutic hypothermia on post-resuscitation myocardial dysfunction has also been reported. We found that mild hypothermia has a profound effect in lengthening the time period of untreated VF before "stone heart" or global ischemic contracture of the left ventricle develops (33). Another report showed that mild post-resuscitation hypothermia ameliorates some of the myocardial dysfunction commonly seen post-cardiac arrest (34).

An important aspect of any pre-clinical model is its relevance to the clinical realm. Translation of such findings, including this pre-clinical report, is always an extrapolation and thereby somewhat speculative. Nonetheless, swine have become the preferred large animal model for both cardiac arrest and myocardial infarct sizing (35). As per the majority of patients with myocardial infarct, swine lack developed large coronary collateral vessels, and their coronary territorial distribution is identical to most humans with the LAD feeding the anterior, septal, and a portion of the lateral left ventricular area (36). Previous investigations have documented that the majority of myocardium is fully infarcted in the corresponding territory within 4 h of an acute coronary occlusion (20). The same process generally takes 12 h in humans, making 1 h in the porcine model equivalent to 3 h in patients (1:3 ratio). We extrapolated this time-course ratio to fit the usual time course for both induction and achievement of target temperature with therapeutic hypothermia, as well as the typical time from acute coronary occlusion to reperfusion. Therefore the 45-min and 4-h periods of coronary occlusion used in this protocol correspond to 2.25 and 12 h, respectively, in the clinical setting. The 45-min reperfusion group in this study would be equivalent to a patient having chest pain for 1 h at home before seeking medical assistance and a 75-min time of first medical contact to reperfusion. Those study subjects not reperfused during the 4-h study period would be equivalent to no reperfusion for 12 h clinically. Time to target temperature in those receiving hypothermia was 45 to 65 min, the clinical equivalent of 2.25 to 3.25 h. This is rapid cooling, but recent clinical trials have shown such timelines to be within the achievable range using cold saline infusion combined with intravascular cooling (30).

Our protocol mimics a realistic and achievable clinical scenario, including a cooling time to 34°C of 2.7 ± 1.0 h, a reperfusion time from vessel occlusion time of 2.3 ± 0.2 h, and a total occlusion time of 12 ± 0 h in the nonreperfused subjects. Although the usual scientific approach is a "bench to bedside" progression, the clinical observation that some interventional cardiologists are still reluctant to perform immediate coronary angiography post-arrest, motivated this "bedside to bench" study.

STUDY LIMITATIONS. Our goal was to seek objective evidence that such an approach may not be optimal for limiting MI size post-arrest, though it is also recognized that not all promising strategies to limit infarct size in animal models have been successful in humans. A second limitation is the use of balloon occlusion to mimic acute thrombotic coronary occlusion. Though used in the past, this model does not reproduce all the clinical milieu of an acute thrombotic event secondary to plaque rupture. Finally, the longer time to achieve the target temperature of 34°C in group B compared with group A (**Table 3**), though not statistically different ($p = 0.06$), could be a confounder in interpreting the infarct size results between these groups.

CONCLUSIONS

Treatment of resuscitated patients should include early coronary angiography for potential emergent reperfusion, while providing hypothermia for both brain and myocardial protection. Providing only early hypothermia, while delaying coronary angiography, is not optimal therapy and results in larger infarctions among those with acutely occluded culprit coronary arteries. On the basis of this translational result in a porcine model, early therapeutic hypothermia and coronary angiography with reperfusion as needed should be considered in all successfully resuscitated out-of-hospital cardiac arrest patients.

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PERSPECTIVES

WHAT IS KNOWN? Post-cardiac arrest care can improve long-term outcomes.

WHAT IS NEW? Which post-arrest patients need both therapeutic hypothermia and concurrent early coronary angiography is debated. This translational porcine study suggests that in the presence of an acutely occluded coronary artery post-arrest, the best strategy is providing early reperfusion and cooling, rather than cooling alone with a plan for delayed catheterization following neurological recovery.

WHAT IS NEXT? Several pilot randomized clinical trials of combining early catheterization and cooling are under way in resuscitated patients suspected of having a cardiac etiology for their out-of-hospital cardiac arrest.

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KEY WORDS cardiac arrest, coronary angiography, hypothermia, myocardial infarction, reperfusion, resuscitation

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