



## Hypothermia Improves Defibrillation Success and Resuscitation Outcomes From Ventricular Fibrillation

[Original Articles: Arrhythmia/Electrophysiology]

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### Abstract

**Background—** Induced hypothermia is recommended to improve neurological outcomes in unconscious survivors of out-of-hospital ventricular fibrillation (VF) cardiac arrest. Patients resuscitated from a VF arrest are at risk of refribrillation, but there are few data on the effects of already existing hypothermia on defibrillation and resuscitation.

**Methods and Results—** Thirty-two swine (mean±SE weight, 23.0±0.6 kg) were divided into 4 groups: normothermia (n=8), mild hypothermia (35°C) (n=8), moderate hypothermia (33°C) (n=8), and severe hypothermia (30°C) (n=8). Hypothermia was induced by surrounding the animal with ice, and VF was electrically induced. After 8 minutes of unsupported VF (no CPR), the swine were defibrillated (biphasic waveform) with successive shocks as needed and underwent CPR until resumption of spontaneous circulation or no response (>=10 minutes). First-shock defibrillation success was higher in the moderate hypothermia group (6 of 8 hypothermia versus 1 of 8 normothermia;  $P=0.04$ ). The number of shocks needed for late defibrillation (>=1 minute after initial shock) was less in all 3 hypothermia groups compared with normothermia (all  $P<0.05$ ). None of the 8 animals in the normothermia group achieved resumption of spontaneous circulation compared with 3 of 8 mild hypothermia ( $P=NS$ ), 7 of 8 moderate hypothermia ( $P=0.001$ ), and 5 of 8 severe hypothermia ( $P=0.03$ ) animals. Coronary perfusion pressure during CPR was not different between the groups.

**Conclusions—** When VF was induced in the setting of moderate or severe hypothermia, resuscitative measures were facilitated with significantly improved defibrillation success and resuscitation outcome. The beneficial effect of hypothermia was not due to alteration of coronary perfusion pressure, which suggests that changes in the mechanical, metabolic, or electrophysiological properties of the myocardium may be responsible.

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There has been a longstanding interest in using induced hypothermia as a tool to help improve neurological outcomes and decrease injury in patients with various neurological conditions, including traumatic brain injury and stroke.<sup>1–3</sup> Animal studies in which brain injury models were used have demonstrated decreased ischemic cellular injury, decreased brain infarct size, and improved functional status from neurological damage in those animals receiving hypothermic treatment; clinical studies have shown that this is feasible and safe.<sup>2–6</sup> Induced hypothermia has also been advocated for various cardiac conditions, including treatment of refractory arrhythmias<sup>7</sup> and attempts to decrease myocardial infarct size in patients undergoing

primary angioplasty for acute myocardial infarction.<sup>8</sup>

Induced hypothermia during cardiac surgery has been used successfully to protect the brain from global ischemia since the 1950s.<sup>9</sup> Patients who have suffered cardiac arrest are also at risk for global neurological and myocardial ischemia; these sequelae result in a poor survival rate.<sup>10</sup> The first successful use of therapeutic hypothermia after cardiac arrest in humans was described in the late 1950s,<sup>9</sup> but it was not until recently that there has been a strong interest in its clinical use. This is in part due to 2 prospective randomized trials<sup>11,12</sup> that demonstrated improved neurological outcomes in patients randomized to hypothermia (32°C to 34°C) after being resuscitated from an out-of-hospital cardiac arrest/ventricular fibrillation (VF) but who remained in a persistent coma on admission. Hypothermia provided improved neurological status and physical function at discharge as well as a mortality benefit in one study.<sup>11</sup> This has led to recent guideline recommendations that all unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was VF.<sup>9</sup>

Few data on the effects of hypothermia on resuscitation exist. Patients who have suffered a cardiac arrest are at increased risk for refrillation<sup>13,14</sup>; thus, patients resuscitated from cardiac arrest and receiving hypothermia may refrillate while being cooled, and additional defibrillating shocks may be required. Furthermore, hypothermia may predispose patients to arrhythmias, particularly VF.<sup>15,16</sup> Therefore, more information on the effect of preexisting induced hypothermia on defibrillation and resuscitation is needed. We have previously found that severe induced hypothermia (30°C) facilitates transthoracic defibrillation in short-duration (30 seconds) VF, with less postdefibrillation ventricular asystole.<sup>17</sup> In the present study, we investigated the effects of preexisting induced hypothermia on defibrillation success and resuscitation outcome in a swine model undergoing prolonged VF.

## Methods

### Animal Preparation

Before the study was initiated, approval was obtained by the University of Iowa Animal Care and Use Committee. We studied a total of 32 swine (*Sus scrofa*) (mean±SE weight, 23.0±0.6 kg). Anesthesia was induced with ketamine 20 mg/kg and acepromazine 0.2 mg/kg administered intramuscularly, followed by inhaled halothane. Pentobarbital injections (2 to 6 mg/kg per hour) together with supplemental halothane (0.5% to 4%) were given through the study to maintain sedation. The animals were intubated and ventilated; arterial blood gases were monitored, and ventilatory adjustments were made to maintain physiological arterial pH and a  $P_{O_2} > 100$  mm Hg. One femoral arterial catheter and 2 femoral venous catheters were inserted and used for continuous arterial blood pressure monitoring, administration of medication/fluids, placement of a pulmonary artery catheter (Swan-Ganz thermodilution catheter), and placement of a pacing catheter for induction of VF.

### Induction of Hypothermia

Animals were randomly assigned to normothermia (37.0°C, typical animal baseline temperature in our laboratory) or cooled to 35°C (mild hypothermia), 33°C (moderate hypothermia), or 30°C (severe hypothermia) depending on prior randomization. The swine were cooled by surrounding the head, thorax, and abdomen with ice. The ice was removed when the swine's temperature fell to 0.2°C to 0.3°C above the target temperature because it was noticed

that the animal's temperature would continue to fall after the ice had been removed from the body. This allowed us to maintain each animal at goal temperature. Once cooled, VF was induced, and the animals were resuscitated as described below. Central venous temperature was measured with the use of the thermodilution catheter. Cooling to 35°C required  $23.3 \pm 3.1$  (SE) minutes, to 33°C required  $41.9 \pm 4.2$  (SE) minutes, and to 30°C required  $85 \pm 3.9$  (SE) minutes.

## VF and Resuscitation

VF was induced by delivery of 60-Hz AC current to the right ventricular apex until VF was confirmed by surface ECG, accompanied by a fall in arterial blood pressure to near zero. The animals then underwent an 8-minute unsupported (no chest compression or ventilation) VF arrest. There were 8 animals in the normothermia group and 8 in each hypothermia group. After 8 minutes of unsupported VF, swine were defibrillated with the use of a commercially available truncated exponential biphasic waveform defibrillator (Philips Medical Systems) and anterior/posterior self-adhesive electrode pads, with successive shocks at 50 J/100 J/150 J/200 J as needed to terminate VF. The initial defibrillation shock and the first set of stacked successive shocks, if needed, were defined as "early" shocks. CPR was then begun, including chest compressions (80 to 100/min) and mechanical ventilation at a rate of 20 to 25 breaths per minute (a rate previously used in our laboratory to maintain more physiological pH and avoid acidosis after cardiac arrest) depending on arterial blood gas determinations. Chest compressions were interrupted for no more than 5 seconds every minute to observe the ECG and arterial pressure. At 1 minute, further shocks were delivered if needed. These shocks were either for refractory VF or for recurrent VF (refibrillation) if it had been previously terminated. We defined these as "late" shocks. One minute was chosen to distinguish between early and late shocks because it is within the first minute that the initial set of stacked successive shocks, if needed, is given per normal Advanced Cardiac Life Support protocol. Epinephrine 1 mg was given intravenously every minute after the first minute of CPR as needed for continuing hypotension (arterial pressure <50 mm Hg). Atropine was given if atrioventricular block or severe sinus bradycardia was seen. CPR was continued until return of spontaneous circulation (ROSC) (systolic blood pressure >60 mm Hg without drug infusion or continued chest compressions) or for 10 minutes. Coronary perfusion pressure (CPP) (diastolic blood pressure minus central venous pressure [CVP]) was monitored continuously. During CPR the CVP was measured during the relaxation phase of CPR. Those animals achieving ROSC were monitored, and hypothermia was maintained for 60 minutes, after which the hypothermic animals were actively rewarmed with the use of heating pads and lamps. Rewarming to the baseline temperature required  $122 \pm 3.6$  (SE) minutes in the severe hypothermia group,  $77.1 \pm 4.3$  (SE) minutes in the moderate hypothermia group, and  $74.3 \pm 4.0$  (SE) minutes in the mild hypothermia group. Hemodynamics were monitored continuously during the 60 minutes after ROSC and until rewarming was complete.

## Survival Protocol

After they were rewarmed, the animals had intravenous catheters removed. They were allowed to recover from anesthesia and were observed for 24 hours. The neurological, cardiac, and physical status of the animal was evaluated with a swine neurological score [18](#) during this time. If evidence of neurological injury was seen, animals were observed for an additional 24 hours. After the observation period (24 hours for normal pigs, 48 hours for those with neurological injury), surviving animals were reanesthetized, and hemodynamic parameters were

remeasured. The animals were then euthanized with intravenous KCl.

## Statistical Analysis

All the statistical analyses for this study were performed with the use of SAS (version 9.1, SAS Institute Inc). Tests of normality were performed for all continuous variables. The distribution of hemodynamic variables was found to be normally distributed so that no transformation of data was needed for analysis. For variables that are not normally distributed, nonparametric methods were used; otherwise, parametric methods of analysis were used. A linear mixed model repeated-measures analysis was used to compare mean arterial pressure (MAP), CVP, heart rate (HR), chest compression rate, cardiac output (CO) by thermodilution, and CPP among the 3 hypothermia groups and the control group at 5 time points, including baseline status, after induction of hypothermia, and at 1, 5, and 10 minutes after initial defibrillation. The fixed effects in the linear mixed model included (1) condition (normothermia, mild hypothermia, moderate hypothermia, severe hypothermia), which is a between-subject factor; (2) time (baseline and after induction of hypothermia for HR, CVP, CO, and temperature; baseline, after induction of hypothermia, and 1, 5, 10 minutes after initial defibrillation for MAP and CPP; and 1, 5, 10 minutes after initial defibrillation for chest compression rate); (3) within-subject repeated-measures factor; and (4) condition-time interaction. [Tables 1 and 2](#) depict the hemodynamic variables measured at each time point for the normothermia and hypothermia groups. Probability values reported for these data were from the test of mean contrast in the linear mixed model analysis. For all statistical analyses, a probability value of  $\leq 0.05$  was considered significant.

**TABLE 1. Hemodynamic Data at Baseline and After Induction of Hypothermia**

	Normothermia	Mild Hypothermia	Moderate Hypothermia	Severe Hypothermia
<b>Baseline</b>				
MAP, mm Hg	65.3±1.4	70.7±2.4	66.4±1.5	61.3±1.0
HR, bpm	145.6±6.5	140.5±10.1	145.6±9.1	128.9±6.4
CVP, mm Hg	6.3±0.6	6.9±0.3	6.9±0.4	7.3±0.4
CO, L/min	5.4±0.3	5.2±0.2	6.1±0.3	4.8±0.5
CPP, mm Hg	46.0±1.1	50.4±2.6	46.6±1.5	40.6±0.8
Temperature, °C	37.0±0.3	36.9±0.2	37.0±0.2	37.3±0.2
<b>Hypothermia*</b>				
MAP, mm Hg	68.3±2.6	64.9±1.6	63.4±1.8	56.6±2.4†
HR, bpm	150.5±5.7	138.5±12.6	132.1±6.1	120.3±9.6
CVP, mm Hg	6.8±0.5	6.1±0.4	6.6±0.3	6.5±0.6
CO, L/min	5.5±0.5	4.7±0.3	4.7±0.3	3.0±0.3†
CPP, mm Hg	48.9±2.3	46.0±1.3	45.6±1.8	41.6±1.8†
Temperature, °C	37.0±0.2	34.9±0.0	33.0±0.0	30.0±0.0
Values are mean±SEM. <i>P</i> value is from test of mean contrast in linear mixed model analysis.				
*After induction of hypothermia in 3 groups or equivalent time in normothermia group, before induction of VF.				
† <i>P</i> ≤0.05, ‡ <i>P</i> ≤0.01, hypothermia vs normothermia.				

**TABLE 1. Hemodynamic Data at Baseline and After Induction of Hypothermia**

**TABLE 2. Hemodynamic Data During CPR**

	Normothermia	Mild Hypothermia	Moderate Hypothermia	Severe Hypothermia
<b>1 Minute*</b>				
MAP	23.8±1.5	25.6±2.4	24.7±1.3	22.5±1.6
Chest compression rate	111.8±2.3	107.3±3.3	109.5±1.5	90.0±7.8‡
CPP	10.5±1.9	11.1±1.6	12.1±1.5	9.0±1.1
<b>5 Minutes*</b>				
MAP	30.8±2.4	38.8±2.5	40.9±2.9†	35.9±2.3
Chest compression rate	106.5±1.5	102.8±4.5	103.4±2.8	88.6±8.5
CPP	9.9±1.3	13.8±2.0	16.5±3.4	13.4±2.6
<b>10 Minutes*</b>				
MAP	29.2±2.9	38.0±2.7	44.7±3.6†	39.2±2.8
Chest compression rate	107.3±3.3	102.0±4.4	102.7±3.4	89.6±8.6
CPP	9.8±2.3	13.0±1.9	15.4±3.5	14.4±2.3
Values are mean±SEM. <i>P</i> value is from test of mean contrast in linear mixed model analysis.				
*Elapsed time of CPR from initial defibrillation.				
† <i>P</i> ≤0.05, ‡ <i>P</i> ≤0.01, hypothermia vs normothermia.				

**TABLE 2. Hemodynamic Data During CPR**

The Kruskal-Wallis test was used to compare the number of early defibrillation shocks, number of late defibrillation shocks, and total shocks delivered among the 4 groups. The amounts of epinephrine and atropine given in each group were also compared by this method. Initial shock success for each hypothermia condition compared with normothermia was analyzed with the Fisher exact test. Trend tests for first-shock defibrillation success and ROSC were performed with the Cochran-Armitage trend test.<sup>19</sup> Trend tests for energy delivered and number of defibrillation shocks were performed with the Jonckheere-Terpstra trend test.<sup>20</sup> All probability values for trend tests were 1-tailed. A sample size calculation was not performed before this experiment was initiated. However, a post hoc sample size calculation was performed for first-shock defibrillation success and is as follows: For first-shock defibrillation success, with 8 normothermic animals and 8 hypothermic animals, Fisher exact test at 0.05 significance has 0.80 power to detect a difference in first-shock defibrillation success if the normothermic groups had 10% success versus at least 87% success in the hypothermia group.

The Kruskal-Wallis test was also used to examine differences among the 4 groups in the amount of early shock energy, late shock energy, and total energy administered to the animals. This analysis was followed by a post hoc test for pairwise multiple comparisons based on the Kruskal-Wallis rank sums.

The log-rank test was used to compare recovery time distribution among the control and mild, moderate, and severe hypothermia treatment groups as well as the survival rates among the 4 groups.

Paired *t* test analysis was used to determine the significance in any change of hemodynamic variables of each surviving animal at baseline and at 24 hours after ROSC. Given the absence of survivors in the normothermia group, no comparison was made between the 4 animal groups.

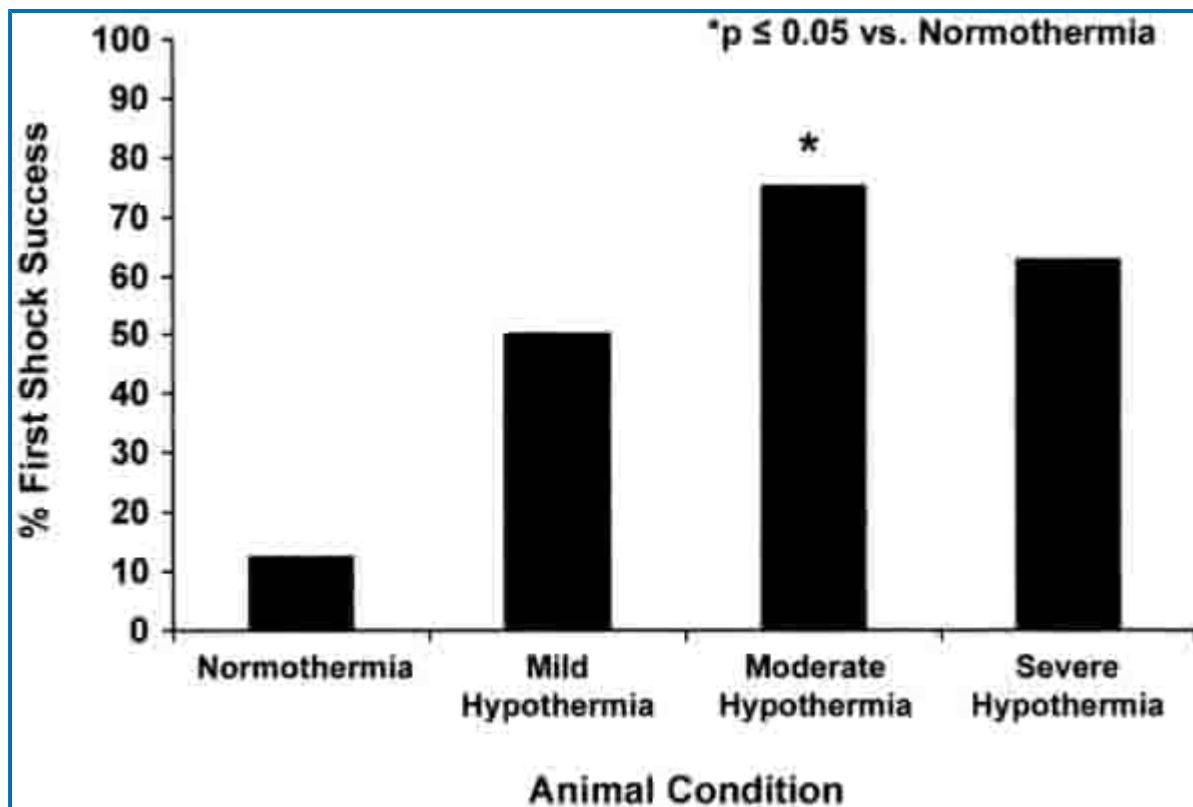
## Results

### Hemodynamic Data

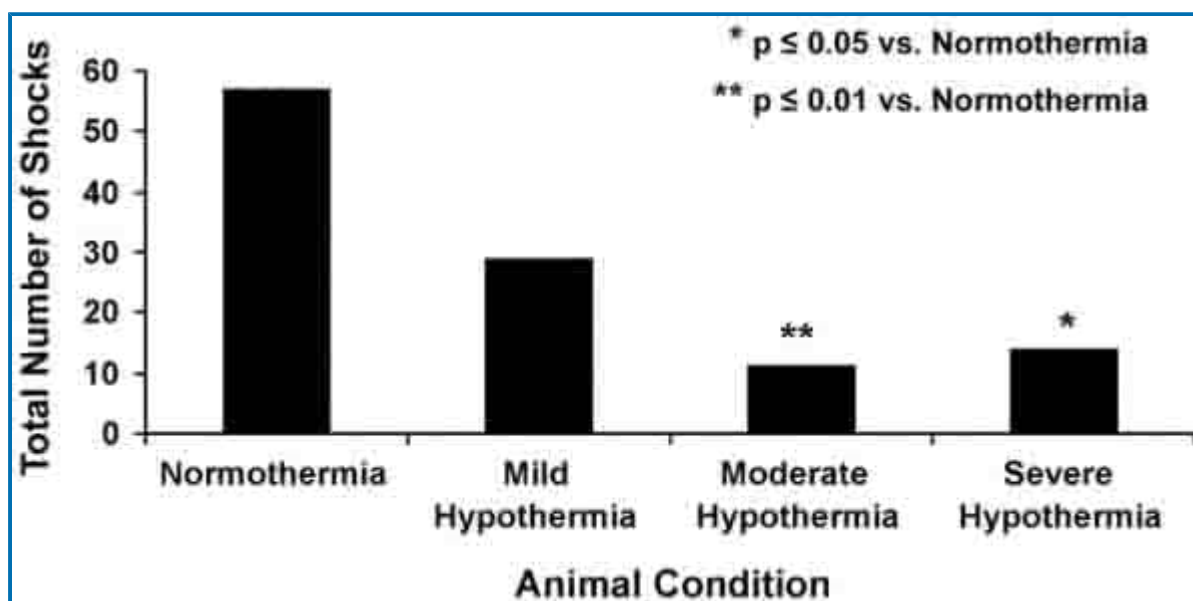
A total of 32 swine (mean±SE weight, 23.0±0.6 kg) were studied and divided into 4 groups: normothermia (n=8), mild hypothermia (35°C) (n=8), moderate hypothermia (33°C) (n=8), and severe hypothermia (30°C) (n=8). Compared with the normothermia group, there was no difference in HR, MAP, CVP, CPP, or CO between the groups at baseline. With induction of hypothermia (but before VF was induced), there was a significant decrease in MAP, CPP, and CO in the severe hypothermia group ( $P=0.006$ ,  $P=0.05$ ,  $P<0.001$ , respectively) compared with the normothermia group (Table 1).

### Defibrillation Data

After 8 minutes of unsupported VF, the first-shock defibrillation success rate, defined as successful termination of VF with the initial 50-J shock in an animal, was 1 of 8 (12.5%) in the normothermia group, 4 of 8 (50%) in the mild hypothermia group, 6 of 8 (75%) in the moderate hypothermia group ( $P=0.04$ ), and 5 of 8 (62.5%) in the severe hypothermia group (Figure 1). The total number of defibrillation shocks delivered was lower in the moderate and severe hypothermia groups ( $P=0.009$  and  $P=0.03$ , respectively) compared with the normothermia group (Figure 2). In the normothermia group, 7 of 8 animals refribrillated after the first minute of resuscitation. In each of the mild, moderate, and severe hypothermia groups, 1 of 8 animals refribrillated. There was a trend toward fewer early shocks in the moderate hypothermia group ( $P=0.06$ ). There were significantly fewer late shocks in all hypothermia groups compared with the normothermia group (mild,  $P=0.01$ ; moderate,  $P=0.004$ ; severe,  $P=0.006$ ) (Figure 3). Trend test analysis found that first-shock defibrillation success rate increased with deeper hypothermia ( $P=0.021$ ). Trend test analysis also found that the number of defibrillation shocks decreased with deeper hypothermia. This was found for total ( $P=0.001$ ), early ( $P=0.007$ ), and late ( $P=0.002$ ) shocks. Hypothermia at any level did not have any effect on whether a perfusing or nonperfusing rhythm occurred after defibrillation. In all groups, including the normothermia group, successful defibrillatory shocks resulted in pulseless electrical activity and required CPR before a resulting perfusing rhythm occurred, with the exception of 1 animal in the moderate hypothermia group. This animal, after successful initial defibrillation and 4 minutes of CPR, achieved ROSC, then redeveloped VF, at which time a 50-J shock was delivered with immediate ROSC and recovery of blood pressure without further CPR or drug support.

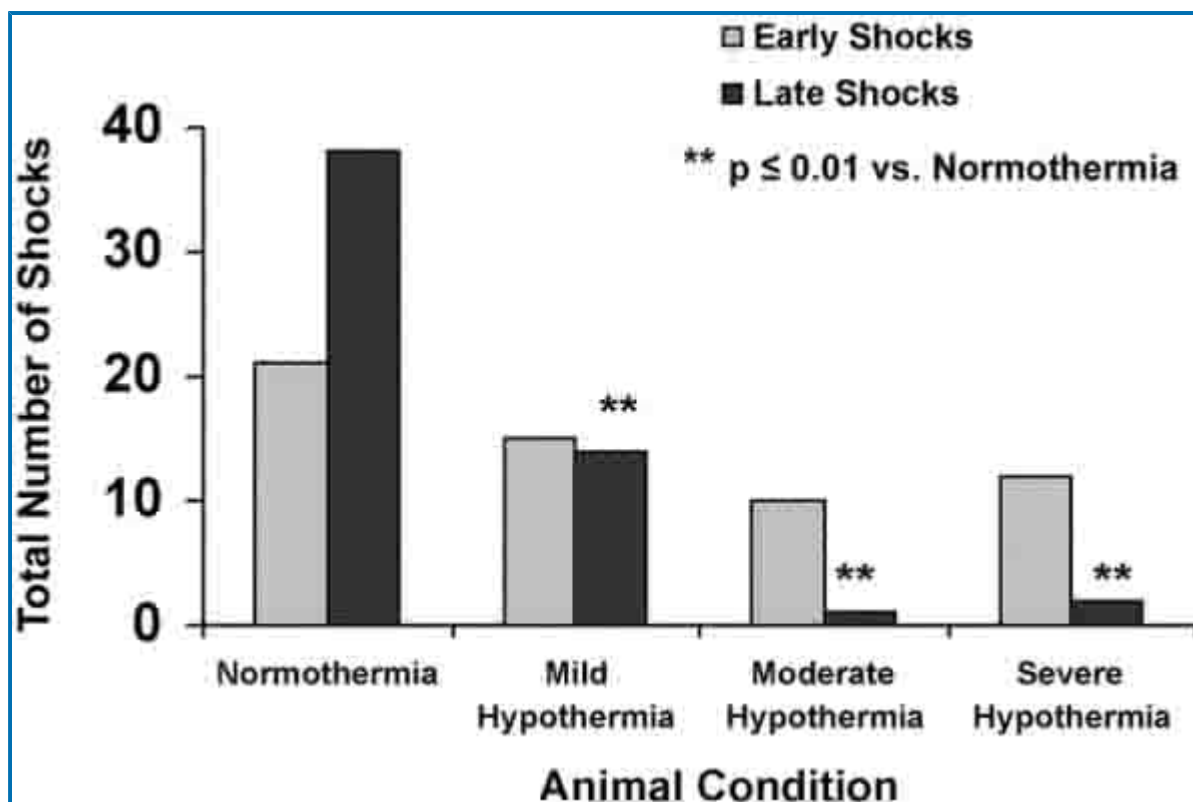


**Figure 1.** Percent first-shock success rate, defined as termination of VF after first defibrillatory shock (one 50-J shock) in each animal temperature condition (n=8 swine per group).



**Figure 2.** Total (cumulative) number of defibrillation shocks delivered during resuscitation in all animals under each temperature condition (n=8 swine per group).



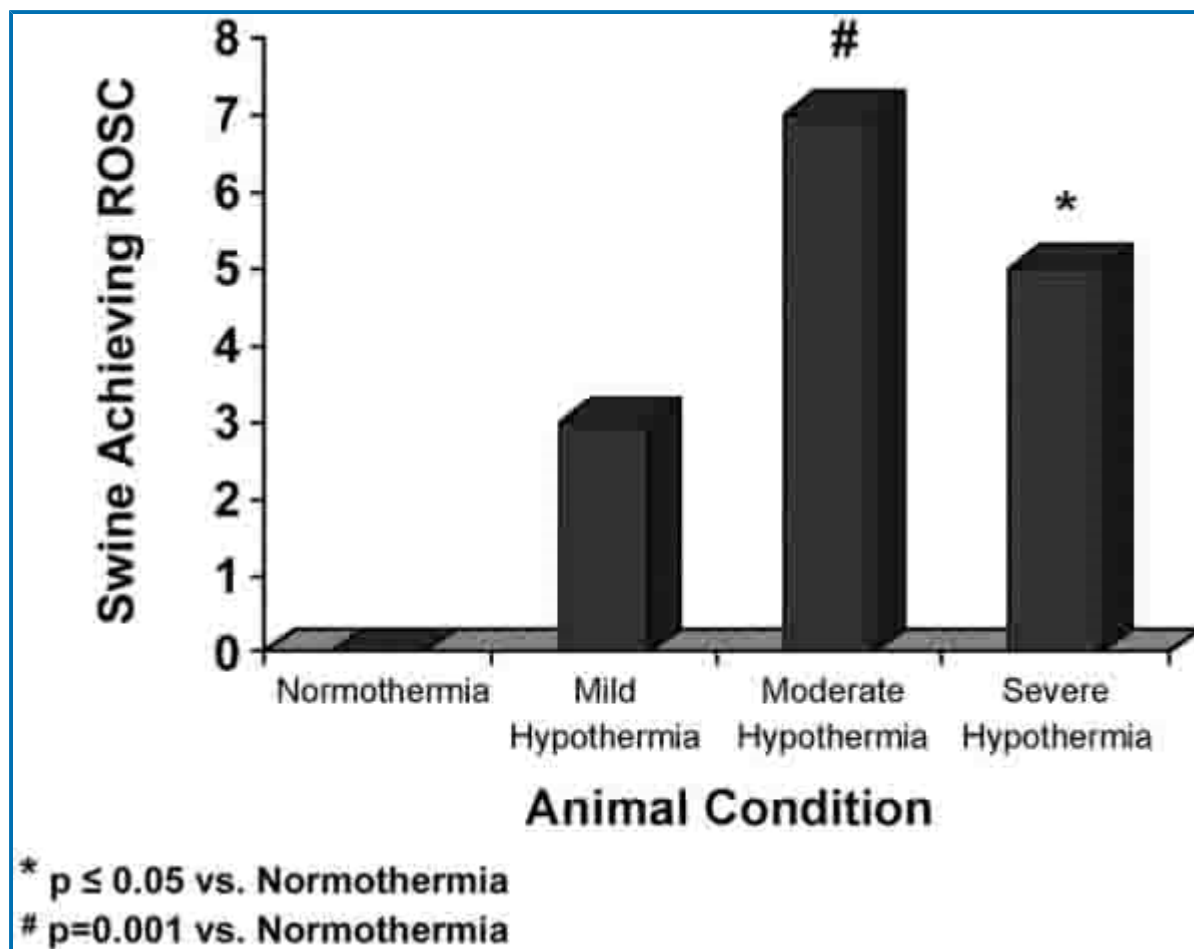


**Figure 3.** Total (cumulative) number of early (first minute of CPR including initial shock) and late ( $\geq 1$  minute after initial shock) defibrillation shocks delivered during resuscitation in all animals under each temperature condition ( $n=8$  swine per group).

The total energy delivered per animal was significantly higher in the normothermia group than in the moderate hypothermia ( $P=0.01$ ) and severe hypothermia ( $P<0.05$ ) groups. The median total energy was 750 J (range, 100 to 3350) for the normothermia group and 50 J for the moderate hypothermia (range, 50 to 150) and severe hypothermia (range, 50 to 350) groups. The same results were observed for late energy (energy delivered  $\geq 1$  minute after initial shock), with values in the normothermia group (median, 475 J; range, 0 to 2850) being significantly higher than those in the moderate hypothermia ( $P<0.05$ ; median, 0; range, 0 to 50) and severe hypothermia ( $P<0.05$ ; median, 0; range, 0 to 200) groups. There was a trend toward less late energy delivered in the mild hypothermia group ( $P=0.07$ ). Smaller differences were observed for the early energy (energy delivered in the first minute of CPR, including initial-shock energy), with a suggested difference between normothermia and moderate hypothermia ( $P=0.07$ ). Trend test analysis found that the amount of delivered energy decreased with deeper hypothermia. This was found for total ( $P=0.001$ ), early ( $P=0.007$ ), and late ( $P<0.001$ ) delivered energy.

#### Resuscitation Data

None of the 8 animals in the control group achieved ROSC compared with 3 (37.5%) in the mild hypothermia group ( $P=0.2$ ), 7 (87.5%) in the moderate hypothermia group ( $P=0.001$ ), and 5 (62.5%) in the severe hypothermia group ( $P=0.03$ ) (Figure 4). Trend test analysis found that the proportion that achieved ROSC increased with deeper hypothermia ( $P=0.002$ ). During CPR, chest compression rate was lower in the severe hypothermia group ( $P=0.01$ ) at 1 minute after defibrillation but was not different at 5 and 10 minutes, and MAP was not different among the 4 groups at 1 minute but was higher in the moderate hypothermia group at 5 and 10 minutes ( $P=0.03$ ,  $P=0.04$ , respectively). CPP was not statistically different between the groups (Table 2). There was no difference in epinephrine and atropine use.



**Figure 4.** Number of swine that achieved ROSC with 24-hour survival in each animal group.

### Survival Data

All animals that achieved ROSC survived 24 hours. Because there were no survivors in the normothermia group, neurological assessment compared with the hypothermia groups could not be made. All animals that achieved ROSC had a neurological score of zero (no neurological deficit)<sup>18</sup> at 24 hours irrespective of their prearrest hypothermia status. Twenty-four hours after ROSC, hemodynamic data were also evaluated. Twenty-four hours after ROSC, there was an average 32.6% drop in CO and 13.3% drop in pulmonary wedge pressure compared with baseline in the moderate hypothermia group ( $P=0.001$ ,  $P=0.02$ , respectively); there were no differences in CPP, MAP, HR, and CVP in this group. There was no statistical difference in any hemodynamic variables in the mild and severe hypothermia groups compared with baseline. Because of the small sample sizes in the groups other than the moderate hypothermia group, no statistical analysis was done between these 3 groups.

### Discussion

In this study, when VF was induced in the setting of moderate or severe hypothermia, resuscitative measures were facilitated with significantly improved defibrillation success and survival. This is the first study to report the benefit of hypothermia in a large-animal model of long-duration cardiac arrest and resuscitation. Our result is encouraging given current recommendations for the use of hypothermia in post-cardiac arrest coma patients, which will result in more widespread use of hypothermia and the likelihood that some hypothermic patients will redevelop VF.

One concern in this study was the inability of any animals in the normothermia group to

achieve ROSC. Historically, in our laboratory we have not had a high rate of ROSC in control/normothermia swine undergoing an 8-minute unsupported arrest. Previous experiments in our laboratory not involving hypothermia have had a ROSC rate in normothermia/control animals undergoing 8 minutes of unsupported VF only as high as 37% (3 of 8 animals) (K.A. Boddicker, MD, et al, unpublished data, 2004). Other investigators have also reported poor success after 8 minutes of unsupported VF.<sup>21</sup> One possible explanation is that our normothermic animals were kept under prolonged general anesthesia (45 minutes after the experimental preparations were complete) before VF arrest was initiated. This was done to create similar total anesthesia times between normothermic swine and the hypothermic swine that needed to be externally cooled before arrest, which required an average of 23 minutes for mild hypothermia up to 85 minutes for the severe hypothermia group. This prolonged prearrest anesthesia, not used by other investigators who were not studying hypothermia, may have contributed to the low ROSC rate in our normothermic animals compared with other studies. It is also possible that our high ventilation rate adversely affected the success of the normothermic animals. Aufderheide et al,<sup>22</sup> in a recent publication, demonstrated that high ventilatory rates may have detrimental effects on the resuscitative process, including a lower rate of ROSC and lower CPP during CPR. In their study (with a resuscitation protocol very different from our own), there was a statistically significant difference in survival between those animals receiving 12 versus 30 breaths per minute, but no survival difference was observed compared with those animals ventilated at 20 breaths per minute, a value closer to our own protocol (20 to 25 breaths per minute). In addition, Aufderheide et al found that those animals ventilated more quickly (20 and 30 breaths per minute) tended to be more alkalotic, with lower  $P_{CO_2}$ , which was not the case with our animals. Any potential adverse effect of the high ventilation rate should have affected all our animals, not just those in the normothermia/control group, because the same rate was used in all.

The increased ROSC rate in our pigs in the moderate and severe hypothermia groups was achieved in part because of faster termination of VF, as evidenced by the increased initial-shock success rate (moderate hypothermia group only). Increased initial-shock success rate in the moderate hypothermia group as well as less total energy delivered in the moderate and severe hypothermia groups may have resulted in fewer toxic effects on the myocardium, resulting in improved outcomes.<sup>14</sup> Van Alem et al <sup>14</sup> observed that refrillation after successful defibrillation in out-of-hospital cardiac arrest is common, and there is a significant inverse relation between the number of refrillations and survival. In all our hypothermia groups, there was significantly less refrillation, requiring fewer late defibrillation shocks.

Prior studies by our laboratory <sup>17</sup> demonstrated that shocks achieved higher success in terminating short-duration (30 seconds) VF in pigs when severe hypothermia (30°C) was induced; in such short-duration VF, defibrillation alone usually resulted in ROSC, with little need for closed-chest compression and no need for epinephrine. The higher shock success rate was seen despite an increase in transthoracic impedance and resultant decline in current delivered to the myocardium compared with normothermic conditions. Similarly, in our present study there was a significant increase in initial first-shock success in the moderate hypothermia group, with a trend toward improvement in the severe hypothermia group. Other investigators also examined the effects of hypothermia on defibrillation.<sup>16,23,24</sup> The results of these investigators vary in their ability to demonstrate defibrillation efficacy in the setting of hypothermia. This may be related in part to different experimental designs, modes of defibrillation, degree of hypothermia used, different animal species, and lack of statistics in one study.<sup>23</sup> Our finding of

improved initial-shock defibrillation is similar to the findings of Arredondo et al,<sup>24</sup> who showed that body hypothermia reduced the transventricular (ie, open-chest model) defibrillation threshold. Unlike our findings, Tacker et al,<sup>23</sup> in a transthoracic defibrillation canine model, found that the defibrillation threshold energy requirement increased 2.5%/°C decrement of body temperature. Ujhelyi et al <sup>16</sup> found that defibrillation energy requirements did not change during hypothermia to 30°C in their transvenous swine defibrillation model.

A striking finding in our study was the significantly decreased rate of refrillation and need for late defibrillation in all hypothermia groups. This is perhaps surprising, given that hypothermia has been found to be arrhythmogenic.<sup>15,16</sup> Ujhelyi et al <sup>16</sup> found that hypothermia prolonged ventricular refractoriness and repolarization, possibly facilitating electric defibrillation by slowing repolarization ion currents. Others have found that hypothermia may slow the automaticity of cardiac pacemaker cells, resulting in slower HRs and improved hemodynamics in some patients with automatic tachycardias.<sup>7</sup> These studies suggest electrophysiological mechanisms by which there was less refrillation in our hypothermic animals.

There may be other beneficial effects of hypothermia, among which may be changes in mechanical or cellular properties of the myocardium. Hypothermia reduces cerebral and myocardial metabolic rate, decreases CO, and decreases cellular energy requirements.<sup>6</sup> Hypothermia changes myocardial substrate selection, resulting in reduced metabolic oxygen consumption via less fatty acid catabolism.<sup>25</sup> Hypothermia may reduce ATP depletion during ischemia and produce mRNA elevation for heat shock protein 70-1, mitochondrial proteins, adenine nucleotide translocator (ANT<sub>1</sub>), and [beta]-F<sub>1</sub>-ATPase, resulting in less mitochondrial dysfunction and increased functional recovery of the heart.<sup>26</sup>

Many of the toxic effects in ischemia/reperfusion injury are related to the NO-superoxide-peroxynitrite pathway and subsequent detrimental enzymatic oxidative cascades that are released, leading to cell death and tissue damage.<sup>27</sup> Although these mechanisms themselves have been well studied in the heart, the effects of hypothermia on these processes in the heart have not been investigated extensively. However, many animal studies have demonstrated the protective neurological effects of hypothermia via the reduction of NO and peroxynitrite stores and by the slowing of many of the enzymatic cascades usually responsible for neurological damage after an ischemic insult.<sup>3,6,28</sup> Specifically, Chatzipanteli et al <sup>28</sup> found in their rat traumatic brain injury model that hypothermia to 30°C decreased both early constitutive and late inducible NO synthase (iNOS) activities. iNOS is an important contributor to both myocardial and cerebral ischemic injury.<sup>27,28</sup> Recently, Scumpia et al,<sup>29</sup> in an endotoxemic rat model, found that hypothermia attenuated iNOS mRNA and iNOS protein production, induced myocardial expression of antiinflammatory cytokines interleukin 10 and 4, inhibited neutrophil aggregation, and attenuated NO-mediated myocardial protein damage as determined by nitrotyrosine. If hypothermia has myocardial effects similar to its effects in the brain, less NO-superoxide-peroxynitrite may result in less toxicity from the subsequent oxidative cascade, hence another possible mechanism for the cardioprotective effect of hypothermia during cardiac arrest/defibrillation/resuscitation.

Our data suggest that hypothermia facilitates resuscitation. Current technology and clinical practice only allow for induction of hypothermia after cardiac arrest and resuscitation. In the future, hypothermia induced during resuscitation, so-called intra-arrest cooling, may become a beneficial way to treat patients during VF arrest, particularly those with refractory arrhythmia.

Abella et al [30](#) recently described a murine model featuring cardiac arrest characterized by ventricular asystole induced by intravenous KCl injection, followed by closed-chest compression and ventilation. They found that those KCl-arrested mice that received intra-arrest cooling to 30°C had greater 72-hour survival than those mice with delayed cooling or normothermia. Thus, although the models are different (murine versus porcine, KCl versus VF arrest, cooling before arrest versus intra-arrest cooling), hypothermia offered substantial benefit in both our studies and those of Abella et al.[30](#) Intra-arrest hypothermia via external cooling is at present impractical in large animals or humans because of the prolonged time required to achieve cooling. In the future, however, intra-arrest cooling may become feasible in a clinical setting as new techniques are developed for rapid cooling, such as large-volume ice-cold intravenous fluids, endovascular devices, and chemical slurries.[8,31–33](#)

## Limitations

There are several limitations to our study. The first is our inability to blind the investigators to the animal's temperature condition. Length of time for cooling and touching of the animal during CPR made it possible for the investigators to differentiate between those animals in the normothermia and hypothermia groups. We tried to account for this by having set chest compression and ventilation rates and a consistent CPR provider. Furthermore, our data demonstrate that there was no difference in CPP achieved during CPR between the 4 animal groups, indicating that there was not a conscious or unconscious bias in our CPR efforts due to the knowledge that hypothermia was or was not present. Another limitation is the fact that our animals had hypothermia induced before the cardiac arrest instead of during the arrest; hypothermia induced during cardiac arrest may not necessarily have the same effect as hypothermia induced before cardiac arrest, although Abella et al [30](#) found it beneficial in their murine model.

## Conclusion

When VF was induced in the setting of moderate or severe hypothermia, resuscitative measures were facilitated, with significantly improved defibrillation success and resuscitation outcome. The beneficial effect of hypothermia was not due to alteration of CPP, suggesting that changes in the mechanical, metabolic, or electrophysiological properties of the myocardium and/or reduction of myocardial oxidative stress may be responsible.

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Key Words: cardiopulmonary resuscitation; defibrillation; hypothermia; ventricular fibrillation

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