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Effects of pre-arrest and intra-arrest hypothermia on ventricular fibrillation and resuscitation

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Abstract

Background—Hypothermia has been shown to improve survival and neurological outcomes for ventricular fibrillation (VF) cardiac arrest. The electrophysiological mechanisms of hypothermia are not well-understood, nor are the effects of beginning cooling during the resuscitation.

Methods and Results—We hypothesized that inducing hypothermia prior to the onset of VF would slow the deleterious changes seen in the ECG during VF and that inducing hypothermia at the start of resuscitation would increase the rates of ROSC and short-term survival in a porcine model of prolonged VF. We randomly assigned 42 domestic swine (27.2 ± 2.3 kgs) to either pretreatment with hypothermia before induction of VF (PRE), normothermic resuscitation (NORM) or intra-resuscitation hypothermia (IRH). During anesthesia, animals were instrumented via femoral cutdown. Lead II ECG was recorded continuously. PRE animals were cooled before the induction of VF, with a rapid infusion of 4° normal saline (30 mL/kg). VF was induced electrically, left untreated for 8 minutes, then mechanical CPR began. During CPR the NORM animals got 30 mL/kg body-temperature saline and the IRH animals got 30 mL/kg 4° saline. In all groups first rescue shocks were delivered after 13 minutes of VF. We calculated the VF scaling exponent (ScE) for the entire 8 minute period (compared using GEE). ROSC and survival were compared with Fisher's exact test. Mean temperature in °C at the onset of VF was PRE=34.7° (±0.8), NORM=37.8 (±0.9), and IRH=37.9 (±0.9). The ScE values over time were significantly lower after 8 minutes in the PRE group (p=0.02). ROSC: PRE=10/14 (71%), NORM=6/14 (43%) and IRH=12/14 (86%); p for IRH vs. NORM=0.02. Survival: PRE=9/14 (64%), NORM=5/14 (36%), IRH 8/14 (57%).

Conclusion—Hypothermia slowed the decay of the ECG waveform during prolonged VF. IRH improved ROSC but not short-term survival compared to NORM. It is possible to rapidly induce mild hypothermia during CPR using an IV infusion of ice-cold saline.

Keywords

heart arrest; cardiopulmonary resuscitation; ventricular fibrillation; hypothermia

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Introduction

Death from cardiovascular diseases (CVD) is a profound clinical and public health challenge, claiming over 910,000 lives per year in the United States.^{1,2} It is by far, the leading cause of death in this and most industrialized nations. Approximately 60% of deaths from CVD (540,000 per year) are sudden cardiac deaths. Approximately 325,000 sudden cardiac deaths occur in the out-of-hospital setting, where the time from the collapse-to-treatment interval is frequently prolonged.³ Survival rates for those who experience out-of-hospital cardiac arrest are dismal.⁴ A meta-analysis of published studies reporting outcomes after out-of-hospital cardiac arrest indicates that survival to hospital discharge is no greater than 6.4%.⁵

Mild induced hypothermia is the first intervention to demonstrate both improved survival and improved neurological outcomes for victims of out-of-hospital sudden cardiac death with an initial ECG rhythm of ventricular fibrillation.^{6,7} One of these studies initiated cooling measures in the prehospital setting *after* return of spontaneous circulation (ROSC).⁷ The many mechanisms by which hypothermia exerts its beneficial effects are as yet, poorly understood. Hypothermia has been shown to reduce the electrical threshold for successful defibrillation.⁸ Slight delays in inducing hypothermia may adversely affect the effectiveness of the therapy.⁹ Better understanding of the electrophysiologic effects of hypothermia during VF, and the utility of beginning cooling before defibrillation may help in optimizing therapy.^{10,11}

We sought to determine the effects of inducing hypothermia prior to the induction of VF, and to determine the effects of inducing hypothermia at the onset of resuscitation in an established porcine model of prolonged VF. We hypothesized that the time-dependent deterioration of the ECG waveform during VF would be slowed by mild hypothermia, when compared to normothermic VF. We also hypothesized that inducing hypothermia at the onset of resuscitation would increase the rates of ROSC and short-term survival when compared to normothermic resuscitation. Our secondary hypothesis was that hypothermia would improve hemodynamics (indicated by exogenous pressor consumption) during the post-ROSC period.

Methods

The University of Pittsburgh Institutional Animal Care and Use Committee approved this study.

Animal Preparation

Forty-two domestic mixed-breed swine of either sex were prepared in a standardized fashion. We sedated the animals with intramuscular ketamine (10.0 mg/kg) and xylazine (4.0 mg/kg). We obtained intravenous (IV) access via a peripheral ear vein with a 21g catheter. We then established a surgical plane of anesthesia using a rapid IV infusion of alpha-chloralose (50 mg/kg), and maintained this with a continuous infusion of the same (10 mg/kg/hr).

We intubated the animals via direct laryngoscopy with a 5-0 cuffed endotracheal tube, and ventilated them with an FiO₂ of 21% using an Ohmeda 7000 ventilator (Ohmeda, BOC Health Care, Madison, WI). Ventilation was begun at a tidal volume of 12-16 cc/kg, a ventilatory rate of 12 breaths per minute, and an inspiration:expiration ratio of 50%. Ventilation was adjusted to maintain eucapnea (end-tidal carbon dioxide 35-45 torr), which we measured with a side-stream capnometer (LifePak 12, Medtronic Physio-Control, Inc., Redmond, Washington). We measured core body temperature by placing an esophageal probe (Bi-Temp Temperature Monitor, Respiratory Supply Products, Inc., Irvine, California) approximately 10 cm into the animals' esophagus. We placed three surface electrodes configured to correspond to a standard Lead II electrocardiogram (ECG) and monitored this continuously. Electrodes were connected to a DAM-50 wide band-pass differential preamplifier, which provided an amplification of 10-

fold near the chest. ECG data were acquired digitally at a sampling rate of 1000 points/second with a commercially available software package (Chart, v.5.3, ADInstruments, Castle Hill, Australia) and were stored for later calculation of the scaling exponent (ScE), a quantitative measure of the VF morphology that we have described in detail previously.¹²⁻¹⁵ In brief, the ScE is a nonlinear dynamical measure of the roughness, or coarseness, of the VF waveform. It is an estimate of the fractal self-similarity dimension of the VF signal. The ScE increases as untreated VF progressively deteriorates from a coarse to a finer appearance over time. For example, after sixty seconds of untreated VF the ScE will be on the order of 1.10, and after twelve minutes it will be approximately 1.40. After 20 minutes of untreated VF the ScE will approach a value of 1.80, while asystole approaches a value of 2.0.

In addition to the ScE, we also calculated the angular velocity (AV),¹⁶ the log of the absolute correlations (LAC),¹⁷ the amplitude spectrum area (AMSA),^{18,19} and the median slope (MS).²⁰ All of these quantitative measures of the ECG waveform have been shown to correlate with VF duration and the probability of ROSC following defibrillation in both animal and human studies. Unlike the ScE, which increases over time, these four measures decrease over time when VF is untreated.

After establishing a surgical depth plane of anesthesia, animals were paralyzed with pancuronium (4 mg initial bolus IV with additional 2 mg boluses as needed). We placed arterial and venous introducers (9 Fr) in the right femoral artery and vein via cutdown, and passed 7 Fr micro-manometer tipped pressure catheters (Mikro-Tip Catheter Transducers SPR-471A and SPC-370-S, Millar Instruments, Houston, Texas) into the ascending aorta and right atrium. Arterial and venous pressures were also monitored continuously with the same data acquisition system used to record the ECG. Coronary perfusion pressure (CPP) was calculated as the aortic pressure minus the right atrial pressure, measured at the end of the relaxation phase of the duty cycle (i.e. just prior to the subsequent downstroke of the Thumper piston, which is analogous to end-diastole in a beating heart). We analyzed an arterial blood gas (ABG) as soon as arterial access was established (i-STAT Portable Clinical Analyzer, Heska Corporation, Waukesha, WI) and repeated this any time ventilator settings were changed. We recorded the anesthesia time (which we defined as the time from the induction of anesthesia to the time VF was induced).

Experimental Design

When the preparation was complete, baseline data were gathered which included; sex, weight, hematocrit and hemoglobin, arterial blood gases, oxygen saturation, end-tidal carbon dioxide, heart rate, systolic and diastolic blood pressures, and blood glucose. We then assigned the animals to one of three groups (n=14 each group) in a block-randomized fashion (in blocks of three) using a code produced at <http://www.randomization.com>. The research team was not blinded as to the animals' group assignment.

PRE—One group had mild hypothermia induced beginning five minutes before the induction of VF, and is designated as the PRE group. Hypothermia was induced by the rapid infusion of 30 mL/kg of 4° C normal saline solution, using a pressurized infusion bag at a pressure of 300 mmHg and delivered via the femoral vein introducer.

NORM—The normothermia group, designated as NORM, did not receive any additional fluid prior to the induction of VF except for the minimal amount of flow needed to keep the ear vein patent. Then, at the onset of resuscitation (mechanical closed-chest compressions and manual ventilation) the NORM group received 30 mL/kg of body temperature normal saline (37° C $\pm$ 1.0°) infused in the same way as the PRE group.

IRH—The intra-resuscitation hypothermia group, designated as IRH, also had no additional fluid prior to the induction of VF. This group was then given a rapid infusion 30 mL/kg of 4° normal saline at the onset of resuscitation, also infused in the same fashion as the PRE group.

After group assignment and a five minute delay, VF was induced transthoracically in all groups with a 3 second, 60 Hz, 100 mA alternating current. VF was confirmed by the ECG and pressure tracings. No animal required more than one shock to induce VF. The VF was then left untreated for 8 minutes. After 8 minutes, external chest compression and ventilation with 100% oxygen was begun using a mechanical resuscitation device (Thumper, Michigan Instruments, Grand Rapids, MI). Compressions were done in the anterior-posterior direction at a rate of 80 per minute, a depth of 5 cm, a 50% duty cycle, and a ratio of 15 compressions to one ventilation. Ventilation tidal volume was fixed at 400 cc per breath.

After 2 minutes of CPR without drugs, epinephrine (0.10 mg/kg), vasopressin (40 U), propranolol (1.0 mg) and sodium bicarbonate (1.0 mEq/kg) were given and CPR continued uninterrupted for an additional 3 minutes. The first rescue shock was then delivered after a total duration of 13 minutes of VF. We used an impedance-compensating, truncated exponential biphasic defibrillation waveform (LifePak 12, Medtronic-Physio-Control, Redmond, Washington) with a fixed dose of energy of 150J for all defibrillation attempts. All countershocks were administered with paddles by one investigator (JJM) to eliminate intra-user variability. If the rescue shock resulted in a return of spontaneous circulation (ROSC) (which we defined as a systolic blood pressure of 80 mmHg sustained for at least one minute consecutively), the animal was given standardized support and survived short-term (at least 20 minutes, to simulate arrival at the hospital after an out-of-hospital cardiac arrest). If this shock failed, 1 minute of mechanical CPR was completed prior to the next rescue shock. This pattern of a rescue shock followed by one minute of CPR before the next shock was repeated for as long as the ECG rhythm was VF. Standard dose epinephrine (0.015 mg/kg) was given every three minutes after the initial drugs, as long as CPR continued.

Animals in which ROSC was not restored and maintained, had resuscitative interventions continued for 20 minutes beyond the start of the resuscitation (i.e. 28 minutes after the induction of VF). Any animal surviving for the 20-minute endpoint was euthanized with a rapid IV injection of 40 mEq of KCl. Thus, the experimental endpoints were either 20-minute survival after attaining ROSC, or 20 minutes of failed resuscitation. If the animal refribrillated, CPR was continued for 1 minute and rescue shock was delivered if rhythm-appropriate (i.e. the ECG rhythm was VF).

Post-ROSC care included initiating pressure support when the animal reached a threshold mean arterial pressure (MAP) of 65mmHg with an intravenous bolus of 250 mcg norepinephrine. MAP was maintained between 65-85mmHg throughout the 20 minutes of survival via the titration of norepinephrine (50 mcg/1mL). We also adjusted the oxygen content of the ventilator to maintain a PaO₂ of at least 100 mmHg and adjusted ventilation rate to maintain a PaCO₂ between 35-45mm Hg. The experimental timeline is shown in Figure 1.

Body temperature was the independent variable in this experiment. The primary dependent variables for this study were the quantitative electrocardiographic VF waveform changes as measured by the five quantitative ECG measures, and the rates of ROSC and 20-minute survival. Secondary dependent variables were CPP and exogenous pressor consumption during the post-ROSC period.

Statistical Analyses

Descriptive data are reported as proportions, and means with standard deviations. Dichotomous variables were compared with two-tailed Fisher's exact test. Continuous variables were

compared with analysis of variance (ANOVA) and repeated measures ANOVA. Because of the redundancy with the five quantitative ECG measures, we only analyzed the ScE for comparative purposes using generalized estimating equations, and splined linear regression (techniques we have described in detail previously).²¹ Because the NORM and IRH groups were treated identically prior to the onset of CPR, we combined these data during the 8 minutes of untreated VF. The alpha error rate for all comparisons was controlled at the 0.05 level.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

All of the baseline measures (sex distribution, weight, hematocrit and hemoglobin, anesthesia time, arterial blood gases, oxygen saturation, end-tidal carbon dioxide, systolic and diastolic blood pressures, and blood glucose) were mathematically similar between groups. The total amount of fluid given during the experiment did not differ between groups. Though the total dose of norepinephrine used during the recovery period (for animals achieving ROSC) for the NORM group (2.85 ± 0.5 mg) was nearly triple that of the PRE (1.05 ± 0.5 mg) and IRH (0.98 ± 0.5 mg), this was not significantly different due to the low number of survivors. The total number of defibrillation attempts was also not different between groups. See Table 1.

Esophageal temperatures (means $\pm$ standard deviations) at the end of instrumentation did not differ across groups (see Figure 2). At the induction of VF, the PRE group temperature had dropped to $34.7^\circ \pm 0.8$ while the other two groups remained relatively unchanged then and throughout the 8 minutes of untreated VF to the start of CPR. After the five minutes of CPR and drug therapy (13 minutes of VF) the PRE group temperature had risen to $35.6^\circ \pm 0.9$, the IRH group dropped to $34.2^\circ \pm 2.3$, and the NORM remained stable at $37.6^\circ \pm 1.1$.

CPPs during CPR did not differ between groups (Figure 3). This indicates that equivalent CPR was done across groups, and that hypothermia did not affect CPP. The GEE for the ScE demonstrated a significant overall difference between the PRE group and the NORM\IRH group for the 8 minutes of VF ($p=0.02$). Splined regression analysis showed that this difference was most pronounced during minutes 3 to 8 ($p=0.001$), as shown in Figure 4. As expected, the other four quantitative measures showed a similar pattern (Figure 5).

The rates of ROSC were 10/14 (71%) for the PRE group, 6/14 (43%) for the NORM group and 12/14 (86%) for the IRH group. Only IRH and NORM were significantly different, with $p=0.02$. Survival occurred in 9/14 (64%) in the PRE group, 5/14 (36%) in the NORM group, and 8/14 (57%) in the IRH group. None of the pairwise comparisons were different (see Table 2).

Discussion

We observed that mild hypothermia initiated prior to fibrillation slowed the decay of the ScE compared to normothermic VF. The mean hypothermia ScE at 8 minutes was 1.32, while the normothermic ScE was 1.44. The mean ScE difference of 0.12 at 8 minutes is clinically meaningful, as the probability of predicting a successful defibrillation at an ScE of 1.30 is 100% sensitive and 76% specific for predicting ROSC. Thus, hypothermia has beneficial electrophysiologic effect by slowing the time-dependent decrease in organization of the VF waveform. This effect helps to explain, in part, the previous findings of Rhee, *et al.* and Boddicker, *et al.* who demonstrated that hypothermia decreased the defibrillation threshold and improved defibrillation success rates.^{8,9}

Our study can be compared to several others that used swine models of VF. Our PRE and IRH groups had mild hypothermia by the time the first rescue shock was delivered, but both had better rates of ROSC than did the mild hypothermia animals in the study by Boddicker, *et al.*⁹, who had only 3/8 (38%). On average, our PRE and IRH also had slightly fewer numbers of shocks (2.6 shocks) compared to the mild hypothermia group in their study (3.6 shocks). Like the Iowa group, we also observed that CPP was not affected by hypothermia.

In another study of similar design that also used 8 minutes of VF, Nordmark, *et al.* gave 30 mL/kg of 4° acetated Ringer's solution begun during CPR and infused over 22 minutes.²² They achieved only a 1.6° drop in temperature, but had 9/10 (90%) of cooled animals achieve ROSC and 8/10 (80%) survive for 180 minutes. The slower rate of infusion during cardiac arrest may have been beneficial, though this remains open for additional research.

While the ROSC rate for the IRH (86%) was significantly higher than the NORM (43%), the PRE (71%) was not, even though this was a 65% relative improvement over NORM. The survival rates did not differ between the three groups. These rates were somewhat lower than expected based on our experience with this model. This raises the concern that perhaps too much fluid given before and during the resuscitation may be detrimental. The increased fluid volume could potentially raise the right atrial pressure, which would decrease the CPP. Since this study did not have a control group that did not receive 30 mL/kg of normal saline, we compared right atrial pressures during CPR between the NORM group and a concurrent control group from another study that was done in our laboratory during the same time period.²³ The mean right atrial pressure for the NORM group was 19.9 ($\pm$ 1.9) mmHg, while the concurrent control group mean right atrial pressure was 19.4 ($\pm$ 3.2) mmHg (the repeated measures ANOVA p-value is 0.61). Thus it would appear that the infusion of 30 mL/kg did not dramatically increase right atrial pressure during CPR. Regardless, examining the effects of various fluid volumes on hemodynamics and post-ROSC outcomes is worthy of additional research. It may also be possible to reduce the fluid volume by combining an infusion with other cooling modalities.²⁴

It may be that delaying hypothermia by as little as 20 minutes after the onset of VF can greatly reduce its effectiveness.²⁵ There are several recent pilot studies demonstrating the feasibility of beginning to induce hypothermia in the prehospital setting. One demonstrated that cooling could be started out-of-hospital immediately after attaining ROSC,²⁵ while two others have shown that cooling could be initiated during CPR.^{27, 28} The American Heart Association Guidelines 2005 do not specifically state when cooling of patients should begin.²⁹ If it can be shown to be safe and effective to initiate hypothermia measures as early as possible, even during CPR, then additional research to optimize early cooling should be explored.

Limitations

Our study has several important limitations. First, we used young pigs that were presumably free of coronary artery disease. Second, the pigs were also anesthetized before the onset of VF. Third, we induced VF suddenly with a transthoracic shock that was not preceded by ischemia. This is a model of sudden dysrhythmic cardiac arrest not ischemia-induced VF. Fourth, if we had shocked the PRE group right at 8 minutes of VF rather than spending 5 minutes doing CPR and giving drugs, the results may have differed. Fifth, we observed only short-duration survival, and thus cannot know what effects PRE and IRH may have had on neurological outcomes. Finally, the research team was not blinded as to which group the animals were assigned to. However, we believe that this was countered by the fact that CPR was done mechanically and the CPPs achieved in all three groups were quite similar.

Conclusions

Pre-arrest hypothermia slowed the decay of the ECG waveform during prolonged VF, as evidenced by the ScE. Intra-resuscitation hypothermia improved ROSC but not survival compared to NORM. Mild hypothermia can be rapidly induced with an IV infusion of ice-cold saline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Experimental timeline of events. Shaded boxes are events common to all three experimental groups. (Epi= epinephrine, Vaso= vasopressin, Bicarb= sodium bicarbonate).

Figure 2.
Esophageal temperatures during various experimental events (reported in °C).

Figure 3. Coronary perfusion pressures (CPPs) in mmHg during 5 minutes of CPR (minutes 8-13 of ventricular fibrillation).

Figure 4.
Scaling exponent (ScE) values during 8 minutes of untreated ventricular fibrillation.

Figure 5.

Quantitative ECG measures during 8 minutes of untreated ventricular fibrillation. Panel A is the angular velocity (AV), panel B is log of the absolute correlations (LAC), panel C is the amplitude spectrum area (AMSA), panel D is the median slope (MS).

Table 1 Baseline and resuscitation characteristics, presented as proportions, means and standard deviations (in parentheses).

Group	Wgt (kgs)	Male (%)	Hct (%)	Hg g/dL	Fluid (mL)	A-time (min.)	Shocks (N)	ETCO ₂ (Torr)	SBP (mmHg)	DBP (mmHg)	pH	pCO ₂ (mmHg)	pO ₂ (mmHg)	O ₂ Sat (%)	Glucose (mg/dL)
PRE	26.5 (2.3)	36%	29.6 (2.8)	10.1 (1.0)	844 (57)	37.1 (7.5)	2.6 (1.6)	39.8 (1.3)	126 (11)	84 (7)	7.44 (.02)	35.9 (2.6)	85.1 (14)	96 (3.3)	137 (23)
NORM	26.1 (1.8)	43%	28.9 (2.4)	9.8 (0.9)	845 (50)	36.9 (10.6)	3.1 (1.6)	39.3 (1.7)	125 (7)	86 (5)	7.45 (.02)	37.5 (3.0)	85.4 (17)	94.9 (4.3)	134 (15)
IRH	26.8 (2.5)	36%	27.6 (3.3)	9.4 (1.1)	832 (53)	36.1 (7.5)	2.6 (1.7)	39.0 (2.3)	122 (9)	82 (5)	7.45 (.04)	35.4 (2.5)	87.9 (14)	97 (1.3)	144 (20)

Table 2

Resuscitation outcomes (ROSC and short-term survival) with p-values from Fisher's Exact Test comparisons.

GROUP (n)	ROSC (%)	P vs. PRE	P vs. NORM
PRE (14)	10 (71%)		
NORM (14)	6 (43%)	P=0.09	
IRH (14)	12 (86%)	P=0.24	P=0.02
	Survival (%)	P vs. PRE	P vs. NORM
PRE (14)	9 (64%)		
NORM (14)	5 (36%)	P=0.10	
IRH (14)	8 (57%)	P=0.50	P=0.16