

## Experimental paper

# The feasibility of inducing mild therapeutic hypothermia after cardiac resuscitation using iced saline infusion via an intraosseous needle<sup>☆,☆☆</sup>

Timothy J. Mader<sup>\*</sup>, Joshua K. Walterscheid, Adam R. Kellogg, Cynthia C. Lodding

Department of Emergency Medicine, Baystate Medical Center/Tufts University School of Medicine, Springfield, MA, USA

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## ABSTRACT

**Objective:** This study was done, using a swine model of prolonged ventricular fibrillation out-of-hospital cardiac arrest, to determine the feasibility of inducing therapeutic hypothermia after successful resuscitation by giving an intraosseous infusion of iced saline.

**Methods:** This study was IACUC approved. Liter bags of normal saline, after being refrigerated for at least 24 h, were placed in an ice filled cooler. Female Yorkshire swine weighing between 27 and 35 kg were sedated and instrumented under general anesthesia. A temperature probe was inserted 10 cm into the esophagus. Ventricular fibrillation was electrically induced and allowed to continue untreated for 10 min. Animals were randomized to one of two resuscitation schemes for the primary study ( $N=53$ ). One group had central intravenous access for drug delivery and the other had an intraosseous needle inserted into the proximal tibia for drug administration. Animals in which spontaneous circulation was restored were immediately cooled, for this secondary study, by means of a rapid, pump-assisted infusion of 1 L of iced saline either through the intraosseous needle ( $n=8$ ), the central access ( $n=6$ ), or a peripheral intravenous catheter ( $n=7$ ) in a systematic, non-randomized fashion. Room, animal, and saline temperatures were recorded at initiation and upon completion of infusion. The data were analyzed descriptively using Stata SE v8.1 for Macintosh.

**Results:** The baseline characteristics of all three groups were mathematically the same. The average ambient room temperature during the experimental sessions was 25.5 °C (SD = 1.3 °C). There were no statistically significant differences between the three groups with regard to saline temperature, rate of infusion, or decrease in core body temperature. The decrease in core temperature for the intraosseous group was 2.8 °C (95% CI = 1.8, 3.8) over the infusion period.

**Conclusions:** Mild therapeutic hypothermia can be effectively induced in swine after successful resuscitation of prolonged ventricular fibrillation by infusion of iced saline through an IO needle.

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## 1. Introduction

Mild induced therapeutic hypothermia is currently recommended for survivors of out-of-hospital cardiac arrest who meet specified criteria.<sup>1,2</sup> It is generally believed that post-resuscitative hypothermia should be induced as early as possible. This notion has led many emergency medical services to initiate this process by a combination of surface cooling and infusion of cold saline

immediately upon return of spontaneous circulation in the pre-hospital setting. The induction of mild therapeutic hypothermia with a rapid infusion of 4 °C crystalloid via peripheral intravenous (IV) has recently been shown to effectively lower body temperature in out-of-hospital cardiac arrest survivors prior to hospital arrival without causing any adverse consequences.<sup>3–5</sup>

Given that timely IV access is not always possible when tending to out-of-hospital cardiac arrest victims, the intraosseous (IO) route of drug administration is now being promoted as a viable first option to facilitate resuscitation.<sup>6</sup> The preference for the IO alternative under these circumstances may be justified since failure to obtain peripheral IV access on the first attempt typically occurs in one out of four patients and successful cannulation of a vessel usually requires 4–5 precious minutes.<sup>7,8</sup>

With the reemphasis on IO placement during out-of-hospital cardiac resuscitation, this study was done to determine if rapid infusion of iced normal saline via IO access is an effective method for inducing therapeutic hypothermia.

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<sup>\*</sup> Corresponding author at: Department of Emergency Medicine, Baystate Medical Center/Tufts University School of Medicine, 759 Chestnut Street, Springfield, MA, USA. Tel.: +1 413 794 1661; fax: +1 413 794 8070.

E-mail address: [timothy.mader@bhs.org](mailto:timothy.mader@bhs.org) (T.J. Mader).

## 2. Materials and methods

An established swine model of prolonged ventricular fibrillation cardiac arrest was used for this study.<sup>9,10</sup> The Institutional Animal Care and Utilization Committee reviewed and approved the protocol. Female Yorkshire swine weighing between 27 and 35 kg were sedated with an intramuscular cocktail of telazol, ketamine, and xylazine. While spontaneously breathing, they underwent endotracheal intubation and a size appropriate venous catheter (20-gauge) was placed in an auricular vein and secured in place. They were then further instrumented under general anesthesia (inhaled isoflurane initially followed by IV propofol): an arterial introducer (8.5 Fr) was placed under direct visualization into the right femoral artery and a venous introducer (8.5 Fr) into the right femoral vein. During the preparation phase, the animals were ventilated on room air, using a volume-cycled ventilator. A nasopharyngeal probe (Type T, Copper-Constantan Thermocouple, AD Instruments, Colorado Springs, CO) was inserted through the mouth and advanced 10 cm into the animal's esophagus.

Immediately before induction of ventricular fibrillation, a 2-mg bolus of pancuronium was given. Ventricular fibrillation was induced by delivery of a 3 s, 60 Hz, 100 mA transthoracic alternating current using a PowerStat variable transformer. Ventricular fibrillation was allowed to continue untreated for 10 min. The animals were then block randomized to one of two resuscitation schemes for the primary study ( $N=53$ ). One group (IV group) made use of the central IV access for epinephrine administration and the other (IO group) had a pediatric IO needle inserted into the proximal tibia for epinephrine delivery. Correct placement of the IO needle was confirmed by marrow aspiration upon insertion and direct examination on necropsy. There were no placement failures though one subject required a second insertion because of a technical problem unscrewing the stylet hub. Both groups received epinephrine (0.1 mg/kg) followed by 2.5 min of mechanical chest compressions before the first 120J rescue shock attempt. After successful rescue shock, standardized post-resuscitative care was provided to a 20-min endpoint. Failed rescue shock was followed by continued mechanical chest compressions with positive pressure ventilation in both groups, repeat doses of epinephrine (0.01 mg/kg) every 3 min, and rescue shock every minute as long as a shockable rhythm persisted.

Animals in which spontaneous circulation was restored were entered into this secondary study and immediately cooled by infusion of 1 L of iced normal saline through one of three routes: IO needle ( $n=8$ ), central line ( $n=6$ ), or peripheral IV ( $n=7$ ). The three arms of this study were completed sequentially (IO, central, then peripheral) in a systematic non-randomized fashion. A sample of



**Fig. 1.** The Zoll Medical Corporation's Power Infuser® fluid resuscitation pump used to standardize the infusion of iced saline across the groups.

animals that were not actively cooled because they failed to achieve return of spontaneous circulation was also included for comparison as the control group. Data from these animals were gathered during continued resuscitation efforts. The control group was composed of a convenience sample of animals that did not achieve return of spontaneous circulation, enrolled either before or after a treatment group animal, so that we had laboratory conditions similar to those present for the treatment group animals.

The 1-L bags of normal saline used for the study were stored in a 1.8 cu. ft. commercial grade refrigerator (Danby model DAR192w; Guelph, Ontario) on the maximum cold setting [mean temperature of 0.14 °C (SD=1.98 °C, range: 6.67 °C)] for at least 24 h and then placed into a cooler with ice on the day of the experiment. Upon return of spontaneous circulation, the room, animal, and saline temperatures were recorded at the initiation of iced normal saline infusion. The infusions were standardized by use of Zoll Medical Corporation's Power Infuser® fluid resuscitation pump (Fig. 1). All infusions were delivered through the same IV tubing attached directly to the 15-gauge IO needle, the femoral introducer, or the peripheral 20-gauge IV catheter.

**Table 1**  
Baseline characteristics.

	IO needle ( $n=8$ )	Central access ( $n=6$ )	Peripheral IV ( $n=7$ )	Control ( $n=7$ )
Weight (kg)	32.9 (30.5, 35.3)	29.8 (27.5, 32.2)	32.9 (30.0, 35.7)	31.9 (29.6, 34.1)
Anesthesia time (min)	27 (22, 32)	26 (21, 31)	21 (18, 24)	26 (20, 32)
End tidal carbon dioxide (mmHg)	41 (40, 42)	40 (39, 41)	41 (40, 43)	42 (41, 42)
Temperature (°C)	38.0 (37.4, 38.6)	37.8 (37.1, 38.5)	37.8 (37.0, 38.6)	37.8 (36.9, 38.7)
Mean arterial pressure (mmHg)	97 (90, 104)	94(80, 107)	102 (88, 115)	101 (95, 107)
Heart rate (bpm)	129 (112, 146)	109 (85, 133)	125 (106, 145)	113 (94, 131)
Blood glucose(mg/dL)	96 (68, 124)	86 (57, 116)	68 (60, 75)	84(55, 113)
Sodium (mequiv./L)	140 (139, 142)	139 (136, 142)	139 (137, 141)	140 (137, 142)
Potassium (mequiv./L)	4.0 (3.8, 4.2)	3.9 (3.7, 4.2)	4.2 (4.0, 4.4)	4.1 (4.0, 4.2)
Ionized calcium (mmol/L)	1.37 (1.31, 1.43)	1.43 (1.41, 1.46)	1.37 (1.30, 1.44)	1.42 (1.37, 1.47)
Hematocrit (%)	29.0 (24.2, 33.8)	27.8 (26.3, 29.4)	26.7 (25.4, 28.0)	26.6 (23.9, 29.3)
pH (units)	7.50 (7.47, 7.54)	7.49 (7.46, 7.53)	7.50 (7.46, 7.54)	7.49 (7.46, 7.53)
Partial pressure of carbon dioxide (mmHg)	39 (37, 40)	38 (36, 40)	38 (34, 41)	38 (36, 41)
Partial pressure of oxygen (mmHg)	87 (75, 99)	99 (91, 106)	91 (82, 100)	91 (80, 101)
Chest compression pressure (mmHg)	48 (45, 51)	63 (40, 87)	59 (55, 63)	54 (44, 65)
Coronary perfusion pressure (mmHg)	66 (54, 79)	53 (33, 73)	54 (35, 72)	29 (11, 47)

All values are group means (95% confidence intervals).

**Table 2**  
Main results.

	IO needle (n=8)	Central access (n=6)	Peripheral IV (n=7)	Total (n=21)	Control (n=7)
Weight (kg)	33 (30.5, 35.3)	30 (27.5, 32.2)	33 (30.0, 35.7)	32 (30.6, 33.4)	32 (29.6, 34.1)
Saline temperature (°C)	4.7 (4.0, 5.3)	4.5 (3.6, 5.3)	5.3 (4.0, 6.6)	4.8 (4.3, 5.3)	NA
Rate (cm <sup>3</sup> /kg/min)	1.8 (1.3, 2.3)	2.4 (1.9, 2.9)	1.6 (1.2, 2.0)	1.9 (1.6, 2.2)	NA
Temperature change (°C)	2.7 (1.8, 3.8)	3.0 (2.0, 4.0)	3.6 (2.3, 4.7)	3.1 (2.6, 3.6)	0.1 (−0.2, 0.3)

All values are group means (95% confidence intervals).

Upon completion of the infusion, the room, animal, and saline temperatures were again recorded. The time required for infusion of the entire liter of normal saline was determined and subsequently used to calculate the infusion rates.

All data were analyzed descriptively using Stata SE v8.1 for Macintosh (College Station, TX). We used Kruskal–Wallis and Wilcoxon–Mann–Whitney Rank Sum tests to examine the differences between the four study groups. We utilized the traditional alpha error rate of 0.05 to determine statistical significance. Mean values by group with 95% confidence intervals were calculated for all outcome variables for reporting results.

### 3. Results

The baseline characteristics of all groups were essentially the same (Table 1). All variables were the same between groups except for a statistically significant difference in the mean coronary perfusion pressure during animal resuscitation between the IO needle group and the controls ( $p=0.019$ ). All animals were female. The average ambient room temperature during the experimental sessions was 25.5 °C (SD = 1.3 °C). All of the IO needles were found to be in correct position on postmortem examination. Table 2 summarizes our main results. There were no statistically significant differences in the temperature change from beginning to end of iced saline infusion between the IO needle, central access, and the peripheral IV groups.

The animals that received IO infusion of iced normal saline had a mean baseline core temperature of 38.1 °C (95% CI: 37.4, 38.9) that decreased to 35.4 °C (95% CI: 34.4, 36.4) by the end of the infusion. The central access and peripheral IV groups had decreases in core temperature of similar magnitude from 38.0 °C (95% CI: 37.0, 38.9) in both groups to 35.0 °C (95% CI: 34.3, 35.6) and 34.4 °C (95% CI: 32.7, 36.1), respectively (Fig. 2). By comparison, the control group had a negligible change in core temperature from 38.3 °C (95% CI: 37.6, 39.0) to 38.2 °C (95% CI: 37.6, 38.8) during a similar 20-min period, however, with ongoing resuscitation efforts. The difference between the groups that were actively cooled and the group

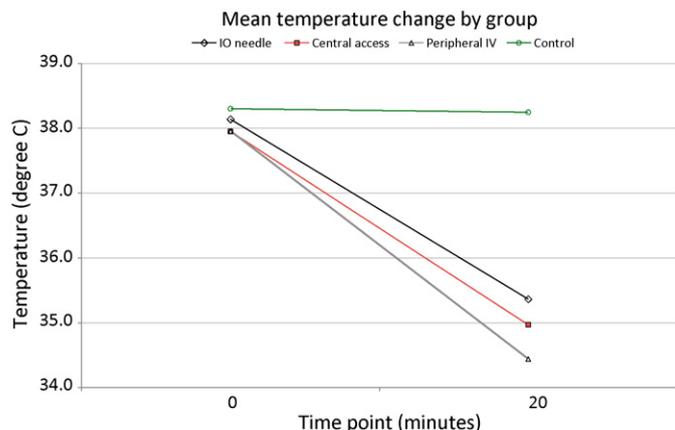


Fig. 2. Mean core temperatures before and after infusion of iced saline by groups.

that acted as the controls was statistically significant ( $p=0.0001$ ) (Fig. 3).

Fig. 4 demonstrates the relationship between the saline temperature, the rate of infusion, and the drop in core temperature in the 21 treatment animals. There was an inverse relationship between the saline temperature at the beginning of the infusion and the magnitude of the core temperature decrease. The colder the saline temperature the greater the drop in the core temperature. When the rate of infusion is examined, there was a direct relationship between the rate of infusion and the magnitude of the core temperature decrease. The faster the infusion rate the greater the core temperature decrease. The relationships are consistent with intuition but the correlations are extremely weak.

### 4. Discussion

A combination of exposure and surface cooling along with a rapid infusion of cold intravenous crystalloid has been shown to facilitate induction of therapeutic hypothermia following return of spontaneous circulation after out-of-hospital cardiac arrest. The results of this study, as illustrated in Table 2 and Fig. 2, demonstrate that there is no difference in the temperature achieved when cooling by infusion of iced normal saline via IO vs. central access vs. peripheral IV.

There was also no demonstrable difference in infusion rates between the three methods (Table 2). While there was a trend showing faster infusion via central line followed by IO needle and

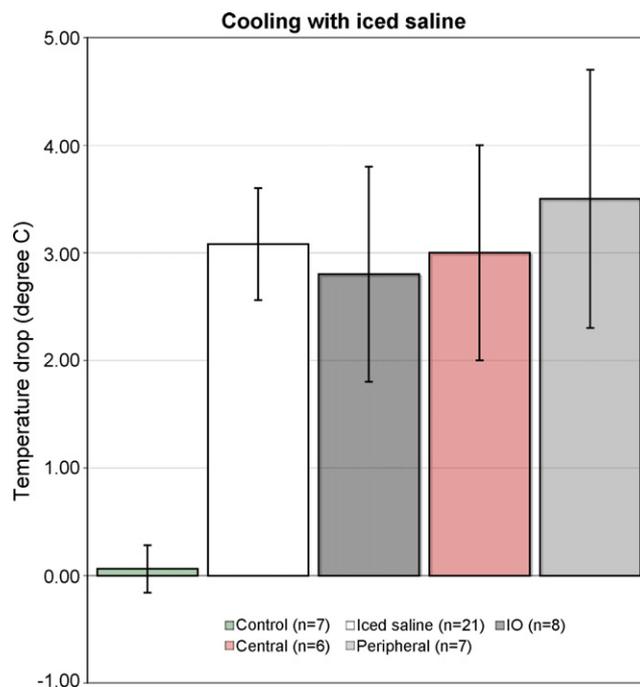
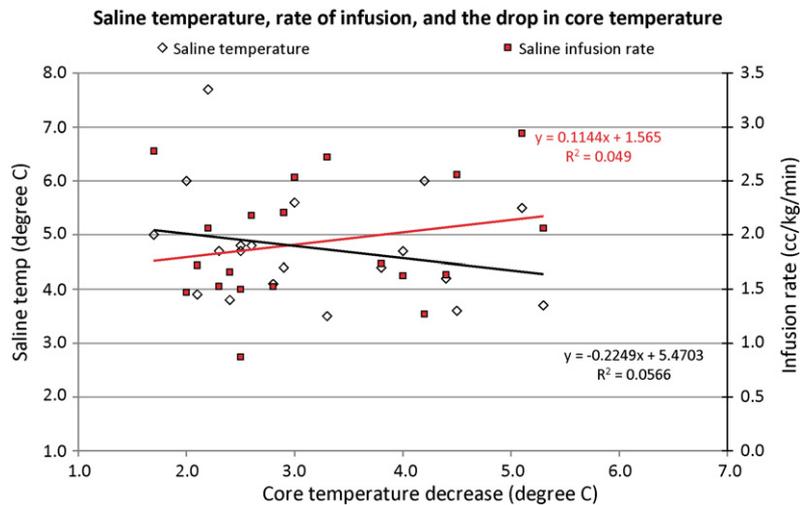


Fig. 3. The magnitude of the temperature decrease for the control group compared to the combined iced saline infusion groups and by the route of administration. The error bars represent the 95% confidence intervals around the mean.



**Fig. 4.** The relationship between infusion rate, saline temperature, and the decrease in core temperature in the 21 treatment animals. There is a trend toward greater core temperature decrease with colder saline and faster infusion rates.

finally peripheral IV, this was not statistically significant. This may have been related to the gauge of the port but more likely is related to the constant infusion rate set on the Zoll Medical Corporation's Power Infuser<sup>®</sup> fluid resuscitation pump used to standardize the infusion of iced saline across the groups. A larger study might indeed demonstrate a difference in flow rate between these three methods with gravity alone, although it is unlikely to be clinically significant.

The volume of iced saline infused in this study was 30.3 cm<sup>3</sup>/kg (SD=4.8 cm<sup>3</sup>/kg). This closely approximates the volume given to humans during induction of therapeutic hypothermia for out-of-hospital cardiac arrest. These patients typically receive 2 L of iced saline, which for a 65 kg adult is equivalent to 30.8 cm<sup>3</sup>/kg.

The fact that therapeutic hypothermia can be as effectively initiated via IO needle as it can through central access has implications for initiation of this therapy in the pre-hospital setting. IO needle access is quick and easy to obtain, which may facilitate resuscitative efforts. When efforts are successful and return of spontaneous circulation is achieved, the access can be used to induce therapeutic hypothermia very rapidly without having to wait for peripheral or central IV access. While it remains to be shown what the optimal time is for initiation of therapeutic hypothermia following out-of-hospital cardiac arrest, it is generally believed that outcomes are improved with early induction of therapeutic hypothermia and rapid achievement of the target temperature. This study provides support for the feasibility and speed of induction of therapeutic hypothermia via IO needle. It should be noted that rapid infusion via all three methods in this study was achieved with the use of a pump (Fig. 1) and not gravity alone.

#### 4.1. Limitations

This experiment was a feasibility study only, conducted in the laboratory using a swine model of cardiac arrest, so the conditions and results may not extrapolate to actual clinical conditions. The study design was non-randomized and not blinded. The sample size in this study was small with only 6–8 subjects in each group. There was limited post-resuscitation hemodynamic assessment and the study ended 20 min after return of spontaneous circulation so there was no data on maintenance of hypothermia. Adjunctive measures such as external surface cooling were not included in this study.

The saline temperature was measured during a set rate of infusion. Longer or shorter durations of infusion as with gravity alone

might affect cooling efficiency. It has been previously noted, for example, that toward the end of each infusion that there was an upward inflection of the temperature curve that could vary in magnitude based by the duration of the infusion.<sup>11</sup>

Further study is needed with a larger sample powered to detect differences between the routes of administration. Additional studies are also needed in human out-of-hospital cardiac arrest patients to test the efficacy under actual clinical conditions.

## 5. Conclusion

In conclusion, therapeutic hypothermia can be effectively induced in swine by infusion of iced saline through an IO needle. The IO needle was as expedient and effective for inducing hypothermia as both central and peripheral IV routes.

## Conflicts of interest

None of the authors have any conflicts of interest to declare.

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## References

- Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003;108:118–21.
- 2005 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112(Suppl.):IV84–8.
- Kim F, Olsufka M, Longstreth Jr WT, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. *Circulation* 2007;115:3064–70.

4. Kamarainen A, Virkkunen I, Tenhunen J, et al. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. *Resuscitation* 2008;79:205–11.
5. Bruel C, Parienti JJ, Marie W, et al. Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest. *Crit Care* 2008;12:R31.
6. Fowler R, Gallagher JV, Isaacs SM, et al. The role of intraosseous vascular access in the out-of-hospital environment (resource document to NAEMSP position statement). *Prehosp Emerg Care* 2007;11:63–6.
7. Lapostolle F, Catineau J, Garrigue B, et al. Prospective evaluation of peripheral venous access difficulty in emergency care. *Intensive Care Med* 2007;33:1452–7.
8. Minville V, Pianezza A, Asehnoune K, et al. Prehospital intravenous line placement assessment in the French emergency system: a prospective study. *Eur J Anaesthesiol* 2006;23:594–7.
9. Mader TJ. Prolonged cardiac arrest: a revised model of porcine ventricular fibrillation. *Resuscitation* 2008;76:481–4.
10. Mader TJ, Kellogg AR, Smith J, et al. A blinded, randomized controlled evaluation of an impedance threshold device during cardiopulmonary resuscitation in swine. *Resuscitation* 2008;77:387–94.
11. Mader TJ. The effect of ambient temperature on cold saline during simulated infusion to induce therapeutic hypothermia. *Resuscitation* 2009;80:766–8.