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Intra-Arrest Transnasal Evaporative Cooling

A Randomized, Prehospital, Multicenter Study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness)

Maaret Castrén, MD, PhD*; Per Nordberg, MD*; Leif Svensson, MD, PhD; Fabio Taccone, MD; Jean-Louise Vincent, MD, PhD; Didier Desruelles, MD; Frank Eichwede, MD; Pierre Mols, MD, PhD; Tilmann Schwab, MD; Michel Vergnion, MD; Christian Storm, MD; Antonio Pesenti, MD, PhD; Jan Pachtl, MD, PhD; Fabien Guérisse, MD; Thomas Elste, MD; Markus Roessler, MD, DEAA; Harald Fritz, MD; Pieterjan Durnez, MD; Hans-Jörg Busch, MD; Becky Inderbitzen, MSE; Denise Barbut, MD

Background—Transnasal evaporative cooling has sufficient heat transfer capacity for effective intra-arrest cooling and improves survival in swine. The aim of this study was to determine the safety, feasibility, and cooling efficacy of prehospital transnasal cooling in humans and to explore its effects on neurologically intact survival to hospital discharge.

Methods and Results—Witnessed cardiac arrest patients with a treatment interval ≤ 20 minutes were randomized to intra-arrest cooling with a RhinoChill device (treatment group, $n=96$) versus standard care (control group, $n=104$). The final analysis included 93 versus 101 patients, respectively. Both groups were cooled after hospital arrival. The patients had similar demographics, initial rhythms, rates of bystander cardiopulmonary resuscitation, and intervals to cardiopulmonary resuscitation and arrival of advanced life support personnel. Eighteen device-related adverse events (1 periorbital emphysema, 3 epistaxis, 1 perioral bleed, and 13 nasal discolorations) were reported. Time to target temperature of 34°C was shorter in the treatment group for both tympanic (102 versus 282 minutes, $P=0.03$) and core (155 versus 284 minutes, $P=0.13$) temperature. There were no significant differences in rates of return of spontaneous circulation between the groups (38% in treated subjects versus 43% in control subjects, $P=0.48$), in overall survival of those admitted alive (44% versus 31%, respectively, $P=0.26$), or in neurologically intact survival to discharge (Pittsburgh cerebral performance category scale 1 to 2, 34% versus 21%, $P=0.21$), although the study was not adequately powered to detect changes in these outcomes.

Conclusions—Prehospital intra-arrest transnasal cooling is safe and feasible and is associated with a significant improvement in the time intervals required to cool patients.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT00808236.

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Key Words: prehospital emergency care ■ hypothermia, induced ■ heart arrest ■ emergency medical services

Therapeutic hypothermia for patients resuscitated from cardiac arrest has been shown to save lives; however, current cooling methods are far from optimal. The most critical gap is the absence of a suitable prehospital method for rapid initiation of cooling that can be started early in the field, even before return of spontaneous circulation (ROSC) is achieved (ie, “intra-arrest

cooling”). Few human studies have been published on the feasibility or safety of intra-arrest cooling, despite considerable animal data that demonstrate a clear superiority for rapid intra-arrest cooling over the accepted post-ROSC cooling currently recommended by the American Heart Association¹ and the International Liaison Committee on Resuscitation.²

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The use of mild therapeutic hypothermia in a hospital setting has been recommended since the publication in 2002 of 2 sentinel reports, both of which demonstrated significant improvement in neurologically intact survival for comatose patients with ventricular fibrillation (VF) or ventricular tachycardia even when cooling was performed hours after spontaneous circulation was achieved.^{3,4} These studies led to increased use of and recommendations for the use of mild therapeutic hypothermia within international guidelines.^{1,2,5} Additional studies have reported beneficial effects of cooling patients with nonshockable rhythms,^{6–9} and the clinical use of cooling is becoming the standard of care for patients who achieve ROSC after a cardiac arrest; however, the use of cooling before ROSC, during the intra-arrest period, has almost no human data to support its recommendation, nor is it mentioned in current guidelines.

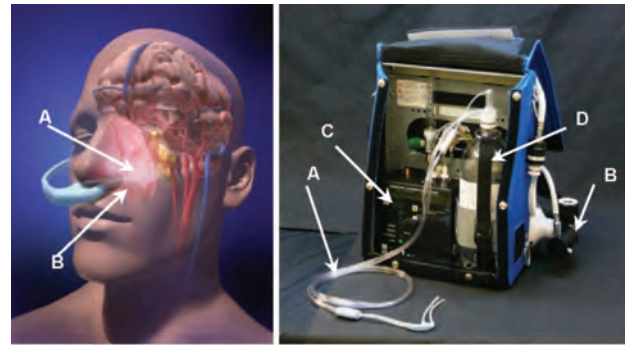
Although human data on effectiveness are absent, multiple animal studies demonstrate that the earlier cooling is initiated, the greater the benefit, including attenuated cerebral injury and increased survival after prolonged ischemia.^{10–13} Moreover, there are animal data to suggest that the “best reperfusion is cool reperfusion,” which implies that intra-arrest cooling may avoid some of the deleterious effects reported as a “reperfusion injury” due to warm reperfusion or warm ROSC after ischemia.^{14–16}

A new method to achieve intra-arrest cooling is transnasal evaporative cooling. A liquid coolant–oxygen mixture is sprayed into the nasal cavity, and the liquid is rapidly evaporated with high-flow oxygen, which results in significant cooling of the nasal passages and brain. The transnasal cooling device is portable, can be used on a patient within minutes of the collapse, and has been demonstrated to be safe for use in humans in the hospital.¹⁷ In animal studies, intra-arrest transnasal cooling has been shown to result in significantly increased rates of ROSC and increased neurologically intact survival.^{18,19} By contrast to currently recommended cooling initiation, which typically starts 90 to 120 minutes after arrest and requires 4 hours or more before a patient reaches target temperature,²⁰ the addition of transnasal evaporative cooling during the resuscitation and subsequent transport to the hospital to standard hospital-based cooling may also reduce the aggregate timing for patients to achieve target temperature. The primary aim of the present study was to determine the safety and feasibility of transnasal evaporative cooling by prehospital rescuers during ongoing resuscitation before achievement of ROSC.

Methods

Study Design

The study was designed as a prospective, randomized trial conducted by the emergency medical system (EMS) personnel in 15 sites in 5 European countries between November 2008 and June 2009. A majority of the sites were 2-tiered, with an advanced life support level as the second tier. All sites had a prehospital physician unit available. The randomization assignments were generated under a randomized permuted-block design, with block sizes of 8, in a 1:1 allocation. Each site was given sequentially numbered sealed envelopes that contained single randomization assignments. Patients were screened for eligibility on arrival of the advanced life support team. The envelope was opened if the patient appeared to be eligible on initial inspection, and the patient was assigned to either intra-arrest transnasal cooling or to no prehospital



A: coolant spray
B: nasal catheter

A: nasal catheter
B: oxygen tank
C: control unit
D: coolant bottle

Figure 1. RhinoChill cooling device.

cooling. Nasal cooling was intended to be continued until transition to systemic cooling in the hospital. Patients in both groups were cooled in the hospital according to institutional standards. EMS and hospital personnel were not blinded during the treatment because the control patients were not treated with sham catheters. Neurological assessment before discharge was intended to be performed by physicians blinded to the treatment given.

The study was approved by the institutional ethics committee of each center. Ethical considerations for treating subjects without their express consent were in accordance with the Helsinki Declaration of 1964, revised in 2008, and the responsible ethics committee for clinical research. The subject’s legal representative was informed of the subject’s study participation as soon as practical, and patients who regained normal neurological function were asked to provide their consent for use of the data.

The study was intended to determine the safety, feasibility, and cooling efficacy of the RhinoChill device (BeneChill, Inc, San Diego, Calif) in the prehospital setting and to assess whether the addition of intra-arrest cooling to hospital-based cooling had any impact on clinically relevant outcome measures such as ROSC rate, survival to discharge, and neurologically intact survival, as well as to gather point estimates of effects for use in the design of future studies. The sample size was selected to establish sufficiently precise measures of safety and feasibility. The study was not powered to address clinical outcome.

Patients

Adults ≥ 18 years of age in out-of-hospital cardiac arrest were recruited during resuscitation by advanced life support personnel. All patients deemed eligible for advanced cardiac life support were included irrespective of rhythm, as long as the arrest was witnessed and cardiopulmonary resuscitation (CPR) was initiated by EMS within 20 minutes of collapse. Time of collapse was estimated by the EMS crew on the scene after information was obtained from bystanders. Patients with trauma, drug overdose, cerebrovascular accident, known coagulopathy, asphyxia or known requirement for supplemental oxygen, and electrocution were excluded, as were those who were very cold on EMS arrival, those who had achieved ROSC before randomization, those with a do-not-attempt-resuscitation order, or those with an intranasal obstruction that made device placement impossible.

Transnasal Cooling Device (RhinoChill)

The RhinoChill equipment consists of a backpack that weighs 12 kg and contains a disposable nasal catheter, a control unit, a 2-L bottle of coolant, and an oxygen tank (Figure 1). The tubing set delivers the oxygen and coolant mixture to the patient. The 10-cm-long nasal catheters are fully inserted through the nostrils along the base of the nasal cavity and have spray ports on the dorsal surface to distribute the coolant in the nasal cavity. The coolant is nebulized by close contact with oxygen at the spray ports. Evaporation of the coolant absorbs heat

from the tissue and rapidly cools the nasal cavity to $\approx 2^{\circ}\text{C}$. The tubing set is connected to a battery-operated control unit that allows the cooling rate to be controlled and automatically switches the system off if the pressure in the nasal cavity exceeds 60 cm H₂O. The cooling efficacy of these parameters was established previously.¹⁷ This system delivers intranasal cooling for 22.5 minutes at an oxygen flow rate of 40 L/min. Additional oxygen tanks or a connection to an ambulance or hospital oxygen supply was required for longer use. The 2-L bottle contained enough coolant for 1 hour of cooling. The equipment is easy to handle. The components of the device can be connected within 30 to 60 seconds, and after it has been turned on, the device is ready to use. All advanced life support crew received a 2-hour training session before clinical use of the device.

Treatment Protocol

In all patients, the resuscitation attempt followed the European Resuscitation Council guidelines. In patients found in VF/ventricular tachycardia and without a palpable pulse after the first shock, intravenous access was established. The airway was secured by endotracheal intubation. In conjunction with these procedures, the patient was assessed for study inclusion. If the patient had not achieved an organized rhythm and palpable pulse by the time the airway was secured, the patient was randomized. In the cooling group, the nasal catheter was placed, and cooling was initiated. Resuscitation attempts continued for at least 30 minutes after EMS arrival.

ROSC was defined as an organized rhythm and palpable pulse that was sustained for at least 20 minutes. Transnasal cooling was continued in the ambulance unless consciousness was regained. Infusion of chilled saline and the use of cold packs were not permitted in the prehospital setting for either group.

All subjects received standard postresuscitation treatment on hospital arrival per the institution's standards. Intravenous sedation, analgesia, and neuromuscular blockade were initiated according to institutional cooling protocols. Where possible, transnasal cooling was continued until systemic cooling was started. Transnasal cooling was discontinued if any device-related serious adverse event occurred. There was no direct way in which aspiration of coolant into the lungs could be determined, because the appearance of aspirated coolant is not different from that of aspirated liquid; however, a chest radiograph and blood gas tests were obtained within 1 hour of admission.

At the time of ROSC and on admission, tympanic temperature was measured with a ThermoScan thermometer (Pro 4000, Braun GmbH, Kronberg, Germany). The tympanic temperature has been suggested to give the best approximation of average cerebral temperature.²¹ Core temperature was recorded according to the institutional protocol at each investigative site either rectally, in the bladder, or intravascularly.

End Points

Safety end points were all adverse events through 24 hours and all serious adverse events through day 7. Time in the intensive care unit and time spent on a ventilator were recorded. Efficacy end points included cooling rates (ie, temperature at ROSC and on hospital arrival and time to target temperature of 34°C), ROSC rate, survival to discharge, and survival with good neurological outcome at hospital discharge. Good neurological outcome was defined as a Pittsburgh cerebral performance category scale of 1 (good recovery) or 2 (moderate disabilities). Bad neurological outcome was defined as patients with cerebral performance category 3 (severe disability), 4 (vegetative state), or 5 (death). The volume of coolant used was also recorded.

Statistical Analysis

Continuous variables that were not normally distributed are reported as medians and interquartile ranges. Categorical variables are reported as counts and percentages. Primary analyses for the efficacy end points were conducted with Pearson χ^2 tests for comparison of binomial proportions. Relative risks (expressed as treatment divided by control) were computed to further characterize the effect sizes. Other analyses were performed with 2-group *t* tests or Wilcoxon rank sum tests for

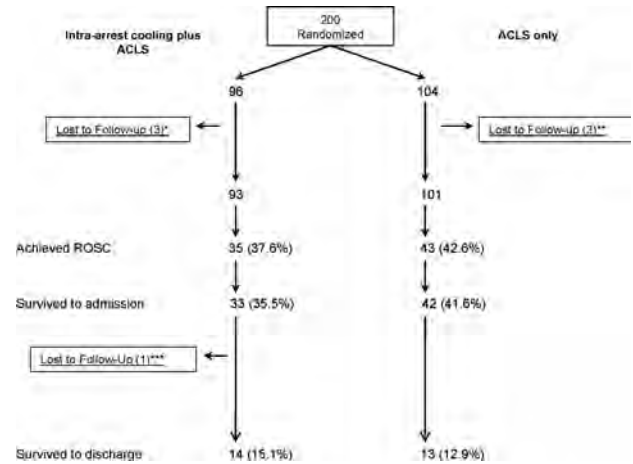


Figure 2. Study flow diagram describing the number of patients enrolled and randomized to advanced cardiac life support (ACLS) with or without intranasal cooling.

*Two patients met predefined exclusion criteria, and consequently, no outcome data were collected; 1 patient was taken to a nonparticipating hospital, and no data were collected for that patient.

**One patient was taken to a nonparticipating hospital, and no data were collected; 1 patient met a predefined exclusion criterion, and consequently, no outcome data were collected; and 1 patient was treated with the RhinoChill device off-protocol, with no data collected.

***One patient met a predefined exclusion criterion, and consequently, no outcome data were collected.

continuous variables and Pearson χ^2 tests for categorical variables. Statistical analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). All probability values were 2-sided, with values less than 0.05 regarded as statistically significant. Because of the exploratory nature of the present study, we did not make statistical adjustments to account for multiple comparisons. Additional post hoc exploratory analyses were conducted that included subgroups defined according to time to CPR and presenting rhythm. Although some patients with predefined exclusion criteria emerged after randomization, all patients for whom outcome data were collected were included in the intention-to-treat analyses (Figure 2).

Results

Two hundred patients were enrolled; for 6 patients (3 from the treatment group and 3 control subjects), no outcome data were collected. One hundred ninety-four patients, therefore, were included in the intention-to-treat analysis (93 were treated and 101 served as controls). Figure 2 shows the participant flow and reasons for exclusion.

Baseline Characteristics and Event Times

There were no significant differences in baseline characteristics (Table 1). There were no differences in the recorded prehospital times between the 2 groups, except for time to a secured airway and randomization, which was significantly later in the treatment group (Table 2). In the treatment group, the airway was secured and patients were randomized a median of 3 minutes later than in the control group ($P=0.03$ and 0.01, respectively). The median time to nasal cooling was 23 minutes (interquartile range 18 to 30 minutes) from collapse. No significant difference was seen in the median time from collapse to ROSC or to hospital arrival (Table 2).

Table 1. Baseline Characteristics

	Treatment (n=93)	Control (n=101)	P*
Age, y, mean	66.1	64.2	0.44
Male sex, n (%)	67 (72.0)	79 (78.2)	0.32
Bystander CPR, n (%)	33 (35.5)	46 (45.5)	0.15
Cardiac cause, n (%)	78/90 (86.7)	86/99 (86.9)	0.97
VF, n (%)	27 (29.0)	32 (31.7)	0.69
PEA, n (%)	19 (20.4)	23 (22.8)	0.69
Asystole, n (%)	47 (50.5)	46 (45.5)	0.49

PEA indicates pulseless electrical activity.

*Two-group *t* test for continuous variables and Pearson χ^2 test for categorical variables.

Adverse Events

Nasal whitening occurred in 13 (14%) of 93 patients during nasal cooling and resolved spontaneously in all 5 resuscitated patients. There was no relationship between longer duration of treatment and nasal discoloration. Epistaxis occurred in 3 patients (3.2%) and was serious in 1 patient with an underlying coagulopathy secondary to hepatic failure. This was the only device-related serious adverse event. Periorbital emphysema occurred 75 minutes into treatment in 1 patient and resolved spontaneously within 24 hours. The total number of serious adverse events that occurred within 7 days was 7 in the treatment group and 14 in the control group (Table 3). There was no difference in hemodynamics (ie, heart rate and blood pressure) on hospital admission between the groups. No significant difference was seen in oxygen saturation (192.5 mm Hg [SD=134.0 mm Hg] for treated patients and 238.4 mm Hg [SD=163.4 mm Hg] for control subjects) or in chest radiograph abnormalities on admission (85% of treated patients and 75% of control subjects).

Cooling Efficacy

Mean tympanic temperatures at ROSC were not significantly different between the groups (35.5°C [SD=0.9°C] in treated patients versus 35.8°C [SD=1.5°C] in control patients, $P=0.40$). On arrival at the hospital, the mean tympanic temperature was significantly lower in the treatment group (34.2°C [SD=1.5°C] versus 35.5°C [SD=0.9°C], $P<0.001$).

Table 2. Event Timing: Median Elapsed Time From Collapse

	Treatment (n=93)	Control (n=101)	P*
First-rescuer CPR	8 (6–11)	8 (5–11)	0.98
ALS arrival	12 (9–16)	11 (8–15)	0.38
IV access	17 (13–20)	15 (12–19)	0.10
Airway secured	19 (14–24)	16 (12–20)	0.03
Randomization	21 (16–25)	18 (15–22)	0.01
Nasal cooling	23 (18–30)
Cooling to ROSC	7 (3–15)
ROSC	32 (28–39)	30 (22–38)	0.19
Hospital arrival	59 (51–75)	60 (42–70)	0.99
Systemic cooling	125 (89–199)	113 (71–200)	0.28

ALS indicates advanced life support; IV, intravenous.

Values are minutes (interquartile range).

*Two-sample Wilcoxon test.

Table 3. Serious Adverse Events Within 7 Days

Serious Adverse Event	Treatment	Control
Acidosis	0	2
Acute myocardial infarction (nonfatal)	0	1
Bleed	1*	1
Cardiac arrest (new)	3	2
Convulsions	1	1
Lethal/long-lasting arrhythmia	1	2
Renal failure	1	2
Sepsis/multiorgan failure	0	3
Total†	7	14

*Device-related epistaxis in patient with an underlying coagulopathy.

† $P=0.23$.

The tympanic temperature decreased an average of 1.3°C from ROSC to hospital arrival (26 minutes). The mean core temperature was also significantly lower in treated patients (35.1°C [SD=1.3°C] versus 35.8°C [SD=0.9°C], $P=0.01$). This was measured rectally in 60%, in the bladder in 35%, and intravascularly in 5% of patients.

In patients who survived until arrival at the hospital ($n=75$), transnasal cooling was initiated within a median of 26 minutes (interquartile range 18 to 34 minutes) from collapse in the treatment group ($n=33$). Systemic cooling at the hospital in the treatment group started at 125 minutes (interquartile range 89 to 199 minutes) after the collapse. In the control group ($n=42$), systemic cooling was initiated at the hospital 113 minutes after the collapse (interquartile range 71 to 200 minutes). Tympanic temperature of 34°C was achieved by a median of 102 minutes (interquartile range 81 to 155 minutes) in the treatment group compared with 291 minutes (interquartile range 183 to 416 minutes, $P=0.03$) in control patients (Figure 3). Median time to target temperature (core) of 34°C in the treatment group was 155 minutes (interquartile range 124 to 315 minutes) versus 284 minutes (interquartile range 172 to 471 minutes) in control patients (Figure 4).

Median transnasal cooling duration was 32 minutes (interquartile range 21 to 60 minutes) for the treated group as a whole and 62 minutes (interquartile range 38 to 140 minutes) for those in whom ROSC was achieved. The volume of coolant used was 1100 mL (300 to 8000 mL) for the entire group and 2000 mL (500 to 8000 mL) for those who achieved ROSC.

Outcome

There were no significant differences in the proportion of patients who achieved ROSC (35 [37.6%] of 93 in the treatment group and 43 [42.6%] of 101 control subjects, $P=0.48$). Survival to hospital discharge is shown in Figure 5. Among patients admitted alive to the hospital, differences in survival to discharge between groups were not significant (43.8% of treated patients and 31.0% of control patients, $P=0.26$, relative risk=1.4). In the subgroup of patients in whom CPR was initiated within 10 minutes (57 of 75 patients, or 76%), the survival to discharge rate was statistically significantly different between groups. Among cooled patients, 56.5% survived to discharge compared with 29.4% of control patients ($P=0.04$, relative risk 1.9). Differences in

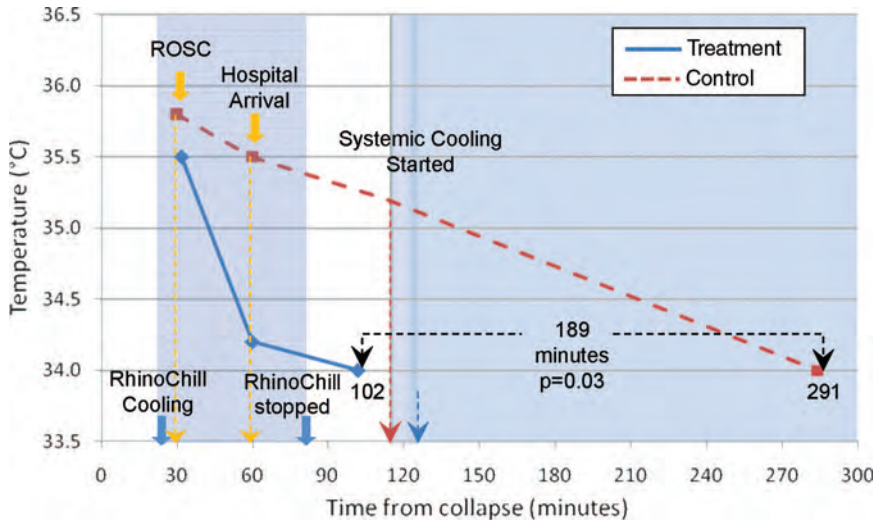


Figure 3. Time to target temperature (tympanic) of 34°C in minutes (median) from the cardiac arrest in the treatment and control groups among those patients admitted to the hospital.

survival to discharge were not significant in the subgroup with VF (n=37) as the presenting rhythm.

Neurologically intact survival to discharge (cerebral performance category 1 to 2) is shown in Figure 6. In the group of admitted patients as a whole, the difference in neurologically intact survival at discharge was not significant (34.4% of treated patients versus 21.4% of control patients, $P=0.21$, relative risk 1.6). Neurologically intact survival to discharge was significantly higher in cooled patients in whom CPR was initiated within 10 minutes of collapse than in control patients (43.5% versus 17.6%, $P=0.03$, relative risk 2.5). Differences in neurologically intact survival were not significant among patients with VF as the presenting rhythm.

In-Hospital Data

No significant differences were seen in cardiogenic shock as the cause of death (3 [9.4%] of 32 patients in the treatment group compared with 11 [26.2%] of 42 control patients), length of hospitalization (24.1 days for treated patients versus 26 days for control patients), days in the intensive care unit (8 days for treated patients versus 11 days for control patients),

and days on a ventilator (4.2 days for treated patients and 8.8 days for control patients).

Discussion

We report the first randomized study to show that prehospital intra-arrest transnasal evaporative cooling is feasible and safe and that early use of cooling is associated with a significant improvement in the time intervals required to cool patients. In the present study, the device was feasible to use during the cardiac arrest, and it did not interfere with the advanced life support protocol. Significant differences in the median time to airway protection and randomization were seen despite the fact that the protocol was the same in both groups until the randomization envelope was open. We have no explanation for these differences. There was no increase in serious adverse events within 7 days in the treatment group. Among device-related adverse events, nasal whitening was the most common event, occurring in 14% of patients. It resolved spontaneously in all resuscitated patients. Epistaxis occurred in 3 treated patients and was serious in 1 patient with an underlying coagulopathy secondary to hepatic failure. This

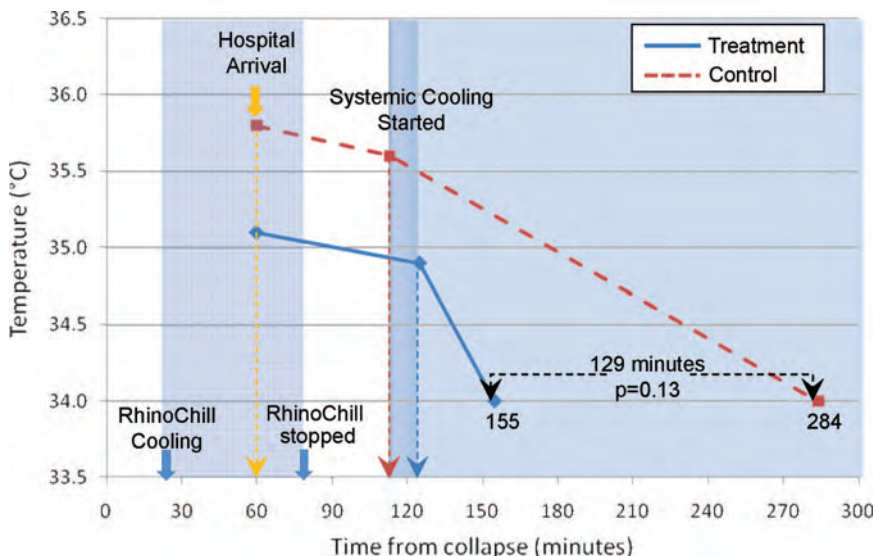


Figure 4. Time to target temperature (core) of 34°C in minutes (median) from the cardiac arrest in the treatment and control groups among those patients admitted to the hospital.

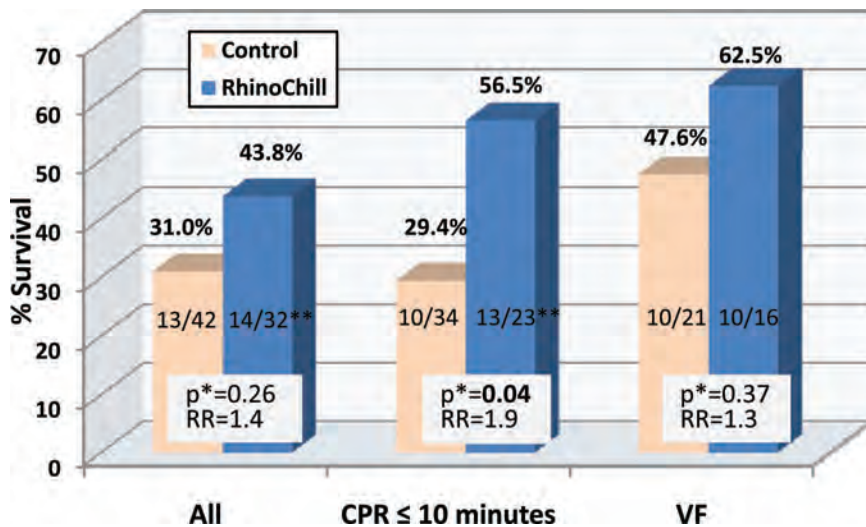


Figure 5. Rates of survival in the treatment and control groups among those patients admitted to the hospital for the entire group, those who received rescuer CPR within 10 minutes, and those with a presenting rhythm of VF. RR indicates relative risk.

*Unadjusted χ^2 test.

**In 1 admitted patient, outcome data were missing.

was the only device-related serious adverse event. The periorbital emphysema that occurred in 1 patient resolved spontaneously within 24 hours. Hypothermia is known to induce a relative bradycardia. This was not seen in the present study despite the fact that the treated patients were significantly colder on hospital admission; there was no difference in their hemodynamics compared with the control patients.

Intra-arrest cooling has been attempted previously in small, nonrandomized studies, and the feasibility of intra-arrest administration of cold saline has been demonstrated. Furthermore, the efficacy of cold saline in reducing core temperature during an arrest has been shown.^{22,23}

The cooling efficacy of cold saline in the prehospital setting after resuscitation has also been investigated.^{24,25} Kim et al²⁴ and Kämäräinen et al²⁵ have demonstrated a reduction in core temperature (esophageal and nasopharyngeal) on patient arrival at the hospital. Kim et al²⁴ showed a trend toward improved survival in patients who presented in VF.

In contrast to the use of cold intravenous saline, evaporative cooling delivered to the nasal cavity will specifically and rapidly induce brain cooling.²⁶ In that animal study, the jugular vein temperature decreased 1.8°C with nasal cooling

compared with 1.3°C with cold saline after 5 minutes of CPR. In addition, a significantly greater coronary perfusion pressure was seen during CPR in the group treated with nasal cooling. With nasal cooling, the body is cooled more slowly, at about the same rate as with intravascular cooling. A brain-body temperature gradient is established, with most of the cold in the primary target organ, the brain.²⁷ The nose and the nasal passages are effective heat exchangers within the body, so that during nasal cooling, cold is transmitted hematogenously by the rich subepithelial vascular plexus to the deep venous sinuses of the brain in the presence of a circulation. Absent a circulation, cold transmission is conductive, across the thin plate of bone at the base of the skull. The efficacy of this cooling technique in cooling the brain in the absence of a circulation has been demonstrated in swine.²⁸

Busch et al¹⁷ have shown that tympanic temperature is lowered by 2.4°C after 1 hour of nasal cooling with the RhinoChill device in resuscitated patients in an emergency department setting. In the present study, prehospital cooling was initiated in the treatment group a median of 23 minutes after collapse, which was 90 minutes before systemic cooling was initiated in control patients. The actual time to apply the

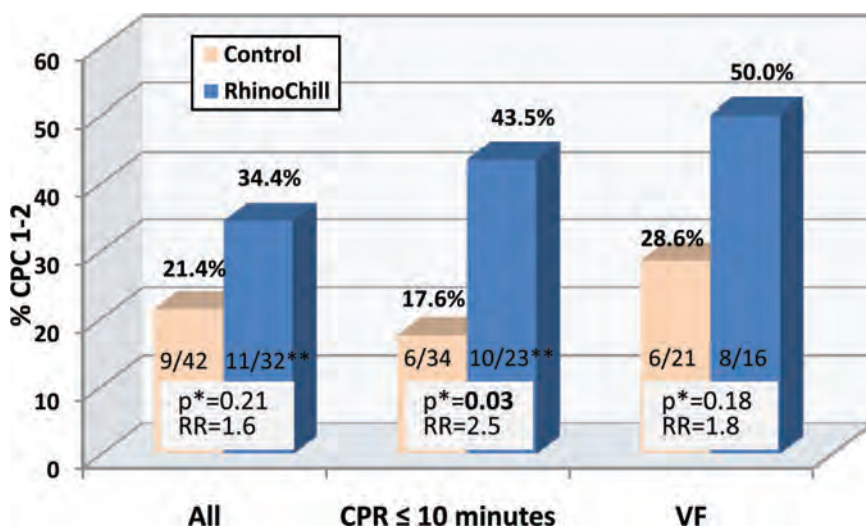


Figure 6. Rates of neurologically intact survival (defined as having a cerebral performance category [CPC] of 1 or 2) in the treatment and control groups among those patients admitted to the hospital for the entire group, those who received rescuer CPR within 10 minutes, and those with a presenting rhythm of VF. RR indicates relative risk.

*Unadjusted χ^2 test.

**In 1 admitted patient, outcome data were missing.

cooling equipment and to initiate cooling (ie, from time of randomization to cooling) was ≈ 2 minutes. Subsequently, the times to a core and tympanic temperature of 34°C were shorter in the treatment group. This 90-minute difference in cooling initiation and the 3-hour difference in reaching the target tympanic temperature or the 2-hour difference in reaching the target core temperature may have influenced survival in these patients.

In the present study, we did not show an improvement in the rate of ROSC in the intra-arrest cooled group. In a porcine cardiac arrest model, Wang et al^{18,29} showed that nasal cooling initiated at the same time as CPR eases resuscitation and improves ROSC rates. Others have also shown a reduction in the electric threshold for successful defibrillation during hypothermic resuscitation^{30,31} and an improvement in the ROSC rate.³² A possible explanation for the failure in the present study to see an improvement in ROSC may be the fact that in our study design, we did not specify exactly when cooling needed to be initiated, for fear of interfering with the resuscitation routine. Therefore, intra-arrest cooling was initiated relatively late during the resuscitation protocol after several shocks had been delivered, a good 15 minutes into CPR, after intravenous access was established, epinephrine had been administered, and endotracheal intubation had been performed. In fact, in contrast to animal studies in which cooling was started at 10 or 15 minutes after the induction of VF, at the same time as CPR, patients in the present study waited on average 23 minutes after collapse before cooling was initiated.

Hypothermia during CPR has been shown to be beneficial for myocardial function in animal models, limiting myocardial infarct size and improving left ventricular function and resuscitation rate,¹⁶ especially with volume-sparing hypothermia.^{16,26} In the present study, there were fewer deaths due to cardiogenic shock in the treatment group. This is consistent with previous animal studies in which ejection fraction recovered faster and more fully in nasally cooled animals.²⁹ In other models of myocardial infarction, myocardial temperature at reperfusion correlated strongly with myocardial salvage.³³

The present study was not powered to detect outcome differences, and in the group as a whole, no significant differences were found; however, it appeared that early nasal cooling and early CPR, when combined, favorably affected outcome. In post hoc analysis of the subgroup of patients in whom CPR was initiated by EMS personnel within 10 minutes of collapse, we saw significantly improved survival, with a 27% absolute increase over patients who received hospital cooling alone. In the same subgroup with early CPR, neurologically intact survival at discharge was also significantly higher in intra-arrest cooled patients, with an absolute increase of 26% over control subjects. In practice, these findings argue in favor of trying to initiate both CPR and nasal cooling as early as possible during the resuscitation process. In the present study, we did not collect data on late-term survival; thus, the outcome results might have been different if patients had been followed up beyond discharge.

The present study has a number of limitations. First and foremost, it was not powered to detect significant differences in outcome. Second, cooling was started very late during resuscitation,

which might be the reason for the lack of differences in ROSC rates. Third, the quality of CPR was not controlled. Fourth, the in-hospital cooling and postresuscitation protocol was not standardized, and in-hospital temperatures were not recorded systematically. Furthermore, patients were not followed up beyond discharge, and neurological function is known to evolve over a 6-month period. In addition, no adjustment for multiple testing was made, which could increase the likelihood of obtaining a statistically significant result. Lastly, blinding during transnasal cooling is impossible, and the discharge assessment may not always have been performed by an individual blinded to the treatment group. Although this would not affect the number of patients surviving to discharge, it could conceivably bias the neurologically intact survival results. In conclusion, we have shown in a randomized study the safety, feasibility, and cooling efficacy of intra-arrest nasal cooling in the prehospital setting.

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Disclosures

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CLINICAL PERSPECTIVE

Therapeutic hypothermia has been shown to benefit survival in survivors of ventricular fibrillation or ventricular tachycardia, even when cooling is initiated with substantial delays in a hospital setting. Current guidelines from the American Heart Association and the International Liaison Committee on Resuscitation recommend cooling all such patients, and the use of cooling is becoming the standard of care in this setting. Many animal studies have shown significant added benefit when cooling is initiated earlier, with maximal benefit achieved when cooling is initiated during the arrest. Intra-arrest cooling has been shown to ease the resuscitation effort, increase resuscitation rates, and improve subsequent myocardial function. To date, intra-arrest cooling has not been studied in randomized human studies, largely because of the absence of methods suitable for use in the field. We have studied a new method of transnasal evaporative cooling that allows cooling to be initiated within minutes of the arrest and that has been shown to cool the brain before circulation is reestablished. The device previously has been shown to be safe for use in humans in an emergency room setting. In a randomized field study, we have shown that this method of cooling can be performed safely during an arrest without derailing the resuscitation effort and that it is relatively easy to implement. Furthermore, we have shown that target tympanic and core temperatures are achieved several hours earlier than with standard hospital-based cooling. Although outcomes are reported, larger studies will be required to determine the extent of the added outcome benefit over hospital-based cooling alone.