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Induction of Therapeutic Hypothermia by Paramedics After Resuscitation From Out-of-Hospital Ventricular Fibrillation Cardiac Arrest

A Randomized Controlled Trial

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Background—Therapeutic hypothermia is recommended for the treatment of neurological injury after resuscitation from out-of-hospital cardiac arrest. Laboratory studies have suggested that earlier cooling may be associated with improved neurological outcomes. We hypothesized that induction of therapeutic hypothermia by paramedics before hospital arrival would improve outcome.

Methods and Results—In a prospective, randomized controlled trial, we assigned adults who had been resuscitated from out-of-hospital cardiac arrest with an initial cardiac rhythm of ventricular fibrillation to either prehospital cooling with a rapid infusion of 2 L of ice-cold lactated Ringer's solution or cooling after hospital admission. The primary outcome measure was functional status at hospital discharge, with a favorable outcome defined as discharge either to home or to a rehabilitation facility. A total of 234 patients were randomly assigned to either paramedic cooling (118 patients) or hospital cooling (116 patients). Patients allocated to paramedic cooling received a median of 1900 mL (first quartile 1000 mL, third quartile 2000 mL) of ice-cold fluid. This resulted in a mean decrease in core temperature of 0.8°C ($P=0.01$). In the paramedic-cooled group, 47.5% patients had a favorable outcome at hospital discharge compared with 52.6% in the hospital-cooled group (risk ratio 0.90, 95% confidence interval 0.70 to 1.17, $P=0.43$).

Conclusions—In adults who have been resuscitated from out-of-hospital cardiac arrest with an initial cardiac rhythm of ventricular fibrillation, paramedic cooling with a rapid infusion of large-volume, ice-cold intravenous fluid decreased core temperature at hospital arrival but was not shown to improve outcome at hospital discharge compared with cooling commenced in the hospital.

Clinical Trial Registration—URL: <http://www.anzctr.org.au>. Unique identifier: ACTRN12605000179639. (*Circulation*. 2010;122:737-742.)

Key Words: cardiopulmonary resuscitation ■ hypothermia, induced ■ emergency medical services ■ ventricular fibrillation

Cardiovascular disease is a leading cause of premature death in developed countries, and many of these deaths occur before hospital arrival because of the onset of ventricular fibrillation (VF).¹ Despite early defibrillation and advanced cardiac life support provided by emergency medical services (EMS), fewer than half of all patients in out-of-hospital cardiac arrest (OHCA) are resuscitated successfully.^{2,3} Among those who have a return of spontaneous circulation and are transported to a hospital, many have sustained severe anoxic neurological injury during the cardiac

arrest, and this injury is a leading cause of subsequent death in the hospital.⁴

Editorial see p 679 Clinical Perspective on p 742

Therapeutic hypothermia (33°C) induced after resuscitation and maintained for 12 to 24 hours has been shown to improve neurological outcomes after resuscitation from OHCA in 2 previous clinical trials^{5,6} and is now recommended for the treatment of patients who remain comatose

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after resuscitation in whom the initial cardiac rhythm is VF.⁷ However, the optimal timing of induction of therapeutic hypothermia is uncertain. Previous studies have used surface cooling with ice packs and/or cooling blankets, and these interventions provided for relatively slow cooling after arrival at the hospital.^{5,6} Laboratory data have suggested that there is significantly decreased neurological injury if cooling is initiated as soon as possible after resuscitation.^{8–11}

Recently, the induction of therapeutic hypothermia with a rapid intravenous infusion of a large volume (30 to 40 mL/kg) of ice-cold crystalloid fluid (LVICF) has been reported as a feasible and effective method in the emergency department that might be applicable in the prehospital setting.^{12,13} However, it is uncertain whether earlier cooling by paramedics improves patient outcomes compared with later cooling after admission to hospital. We therefore conducted a prospective, randomized controlled trial comparing paramedic cooling with hospital cooling in adults after resuscitation from OHCA to determine whether this intervention improves outcome at hospital discharge compared with cooling initiated after hospital arrival.

Methods

This study was a prospective, randomized controlled trial undertaken in Melbourne, Australia, between October 2005 and November 2007. This city has a population of ≈ 4.0 million, with 10 government and 2 private hospitals that receive patients after resuscitation from OHCA.

The EMS in Melbourne is 2-tiered, with ≈ 900 paramedics who are authorized to practice limited advanced cardiac life support skills including defibrillation, insertion of a laryngeal mask airway, and administration of intravenous epinephrine. In addition, there are 180 intensive care paramedics who are authorized to undertake endotracheal intubation and administer a wider range of intravenous drugs during cardiac arrest, such as amiodarone and sodium bicarbonate. Mechanical chest-compression devices and airway impedance systems are not used. After return of spontaneous circulation, intensive care paramedics may administer midazolam and pancuronium to facilitate ventilation. The intensive care paramedics are dispatched to patients with suspected critical illness including cardiac arrest. In addition, firefighters in the inner area of Melbourne are equipped with defibrillators and are also dispatched to patients with suspected cardiac arrest.¹⁴ Paramedic patient care records are electronic, and all patients with OHCA have data stored in the Victorian Ambulance Cardiac Arrest Register. This register has been described in detail previously.² All "call received" and "EMS arrival" times are collected electronically. The "collapse to call" time was estimated after discussion with bystanders, and the "EMS arrival to return of spontaneous circulation" time was recorded by paramedics.

Cardiac arrest management by paramedics follows medically determined, written clinical practice guidelines without online medical control, and these follow the recommendations of the Australian Resuscitation Council (available at www.ambulance.vic.gov.au/Paramedics/Qualified-Paramedic-Training/Clinical-Practice-Guidelines.html). During cardiopulmonary resuscitation (CPR), ambient-temperature lactated Ringer's solution is administered during drug delivery, and a 10-mL/kg fluid bolus is administered if pulseless electric activity has developed. Patients 15 to 17 years of age are treated according to adult clinical practice guidelines and are transported to an adult hospital emergency department. For the present study, all emergency departments and critical care units in the receiving hospitals agreed to adhere whenever possible to the study guidelines, including the maintenance of therapeutic hypothermia at 33°C for 24 hours.

Patients were eligible for enrollment if they were assessed by paramedics as having all the following: OHCA with an initial cardiac rhythm of VF, return of spontaneous circulation, systolic blood pressure >90 mm Hg, cardiac arrest time >10 minutes, age ≥ 15 years, and

intravenous access available. Patients were excluded if they were not intubated, were dependent on others for activities of daily living before the cardiac arrest event, were already hypothermic (temperature $<34^\circ\text{C}$), or were women who were obviously pregnant.

In all patients, ventilation with 100% oxygen was continued with a target end-tidal CO_2 of 35 to 40 mm Hg. An epinephrine infusion was commenced if the systolic arterial blood pressure was less than 90 mm Hg, with a target systolic blood pressure of 100 mm Hg. Temperature was measured with a tympanic temperature probe (Braun Pro3000 type 6014, WelchAllyn Inc, Skaneateles Falls, NY).

The treating intensive care paramedics randomized eligible patients by opening an opaque, sealed envelope that indicated treatment allocation. The envelope allocation was computer randomized and allocated in blocks of 10 to each intensive care paramedic unit.

In addition to usual care, patients allocated to paramedic cooling received intravenous midazolam (0.1 mg/kg) and pancuronium (12 mg) to suppress shivering. An infusion of up to 2000 mL of ice-cold lactated Ringer's solution was commenced at 100 mL/min during transport to hospital by use of a standard infusion set and a pressure bag inflated to 300 mm Hg. This fluid was carried in an insulated container with a thermometer to ensure that the fluid temperature was $<8^\circ\text{C}$. If pulmonary edema developed during or after the infusion (as demonstrated by oxygen desaturation with froth visible in the endotracheal tube), intravenous furosemide 40 mg IV was indicated. On arrival at the hospital, patients received a further 10- to 20-mL/kg rapid infusion of ice-cold lactated Ringer's solution administered by the attending emergency physician.

Patients allocated to hospital care received standard prehospital therapy, including intravenous midazolam (0.1 mg/kg) only if required to facilitate assisted ventilation. Pancuronium was only administered if midazolam was insufficient to control ventilation. Active warming measures were not permitted. On arrival at the hospital emergency department, standard-care patients received sedation, a neuromuscular blocking agent, and a rapid infusion of 40 mL/kg ice-cold lactated Ringer's solution to induce therapeutic hypothermia.

In all patients, surface cooling was commenced in the emergency department or the intensive care unit with a target temperature of 33°C maintained for 24 hours. Core temperature after arrival at the hospital was measured with bladder temperature probes. In 2 hospitals, specialized cooling machines that incorporated adhesive skin pads were used (Arctic Sun, Medivance, Louisville, Colo). In the remaining hospitals, surface cooling with ice packs was used. After 24 hours, patients were rewarmed at 0.25°C per hour. All other aspects of patient management were at the discretion of the treating physicians. In general, patients with ST-segment elevation on ECG underwent immediate cardiac catheterization.

Before hospital discharge, patients were evaluated by a rehabilitation physician who was unaware of the study allocation, and discharge direction was determined. Patients who were discharged directly home or to a rehabilitation facility were considered to have a favorable outcome. Patients who died or who were discharged to a long-term nursing facility, either conscious or unconscious, were considered to have an unfavorable outcome.

Statistical Analysis

The primary outcome measure for the present study was the proportion of patients with a defined favorable outcome. The sample size was calculated to detect a change in favorable outcome from 45% to 60%. This required a sample size of 372 patients to achieve 80% power at an α -error of 0.05. There was a planned interim analysis of the outcomes after 200 patients had been enrolled. $P < 0.001$ was designated as the threshold for stopping the study if there was evidence of significant benefit or harm in either of the study groups.

The secondary outcome measures were core (bladder or esophageal) temperatures at hospital arrival, the development of prehospital pulmonary edema, and recurrent prehospital cardiac arrest after enrollment. All patients allocated to each group were considered as composing the intention-to-treat population for all primary and secondary analyses. Analysis of the primary outcome of favorable survival was performed with the χ^2 test.

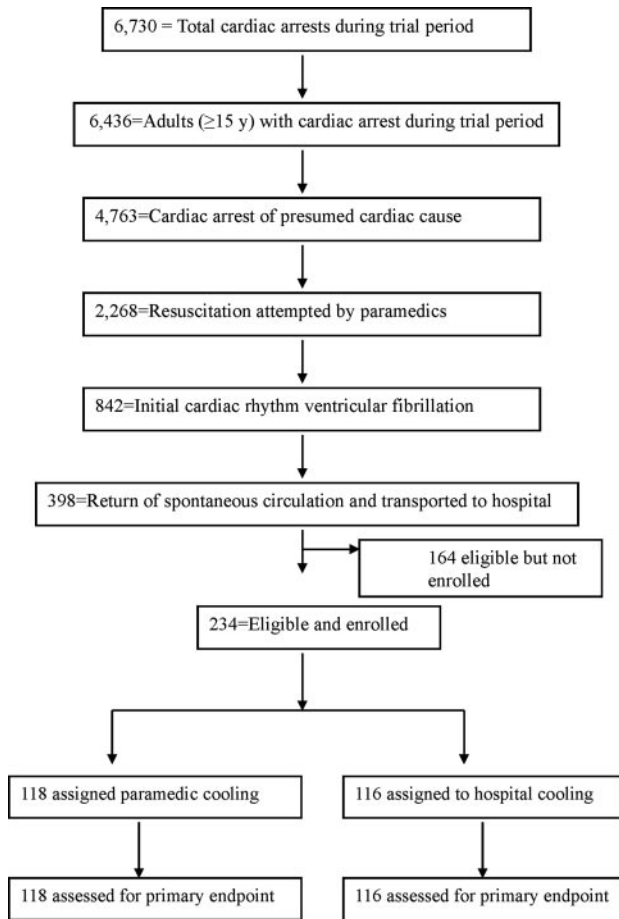


Figure 1. Trial profile.

Additional binomial variables were expressed as proportions and 95% confidence intervals (exact binomial), and groups were compared by χ^2 tests. Variables that approximated a normal distribution were summarized as mean \pm SD, and groups were compared with *t* tests. Nonnormal variables were summarized as median and first and third quartiles, and groups were compared with Mann-Whitney rank sum tests. All reported probability values are 2-sided. The statistical software used was STATA (version 10.0, Stata Corp, College Station, Tex).

At the interim analysis of the first 200 patients, the Steering Committee noted that there was no difference in the primary outcome measure and that it was extremely unlikely that such a difference would emerge between the groups. Therefore, the study was stopped because of futility after 234 patients had been enrolled.

Ethical Issues

The study protocol was approved by the ethics committee of Monash University, Victoria, and the institutional ethics committees at each receiving hospital. The requirement for informed patient consent was waived in accordance with Australian government regulations. These regulations permit nonconsent enrollment of unconscious patients if the study is approved by an institutional ethics committee and next-of-kin or surviving patients are informed of the trial as soon as possible after enrollment (see http://www.nhmrc.gov.au/publications/ethics/2007_humans/section4.4.htm).

Results

Between October 2005 and December 2007, a total of 6730 patients with OHCA were attended by EMS personnel. Figure 1 shows the numbers of patients considered for enrollment. Of 398 patients who were eligible for enrollment, 234 were

Table 1. Baseline Characteristics of the Patients

Characteristic	Paramedic Cooling: Group 1 (n=118)	Hospital Cooling: Group 2 (n=116)	P*
Age, y, mean (SD)	63.4 (16.3)	63 (14.5)	0.83
Male sex, %	83.1	86.2	0.50
Witnessed arrest, %	89.8	83.6	0.16
Bystander CPR, %	68.8	67.0	0.77
Time from collapse to call, min, median (Q1, Q3)	2 (2, 2)	2 (2, 2)	0.08
Time from call to paramedic arrival, min, mean (SD)	8.4 (3.1)	8.9 (3.3)	0.20
Time from paramedic arrival to ROSC, min, mean (SD)	15.5 (8.7)	14.6 (7.6)	0.43
Time from collapse to ROSC, min, mean (SD)	25.9 (9.2)	26.0 (8.7)	0.89
Defibrillation, median No. (Q1, Q3)	4 (2, 7)	4 (2, 6)	0.94
Epinephrine, mg, median (Q1, Q3)	2 (1, 4)	3 (1, 4)	0.65
Ambient-temperature fluid administered during CPR, mL, mean (SD)	928.6 (552.2)	1007.1 (567.1)	0.31

ROSC indicates return of spontaneous circulation.

*P calculated by *t* test, χ^2 test, or Mann-Whitney rank sum test.

randomly allocated to either paramedic cooling (118 patients) or hospital cooling (116 patients).

The baseline characteristics of the patients are shown in Table 1. The 2 groups were similar in the major characteristics associated with outcome after cardiac arrest, including age, sex, bystander CPR, EMS response time, number of defibrillations, dose of epinephrine, and total cardiac arrest time.

Interventions

Of the 118 patients allocated to paramedic cooling, 57 (48%) received 2000 mL, 11 received 1500 to 2000 mL, 37 received 1000 to 1500 mL, 5 received 500 to 1000 mL, and 8 received no ice-cold fluid. The reason for administration of <2000 mL was close proximity to the hospital with a transport time <20 minutes. Of the 116 patients allocated to hospital cooling, 1 received 2000 mL of ice-cold fluid because of a protocol violation.

The patient treatment and vital signs at enrollment and hospital arrival are shown in Table 2 (excluding the results of the 1 patient in the standard-care group who received LVICF). The patient bladder or esophageal temperatures measured on arrival and after 30 and 60 minutes in the emergency department are also shown. This demonstrates that patient temperatures in the 2 groups became similar within 60 minutes of emergency department arrival. Temperatures during the first 36 hours are shown in Figure 2. The initial reading is the first temperature recorded in the emergency department. This demonstrates that after the first 30 minutes, the 2 groups had similar temperatures, and there were no subsequent significant differences between the groups during the initial 36 hours.

Patient Outcomes

The outcomes of the patients at hospital discharge are shown in Table 3. The rate of favorable outcome was 47.5% in the

Table 2. Vital Signs

Variable	Paramedic Cooling: Group 1 (n=118)	Hospital Cooling: Group 2 (n=116)	P*
EMS temperature on scene, °C	35.9 (1.0)	35.8 (0.8)	0.63
EMS temperature on hospital arrival, °C	34.6 (1.3)	35.4 (1.0)	0.01
Temperature in emergency department on arrival, °C	34.4 (1.2)	35.2 (1.0)	0.001
Temperature in emergency department 30 min after arrival, °C	34.4 (1.2)	34.8 (1.0)	0.03
Temperature in emergency department 60 minutes after arrival, °C	34.7 (1.1)	34.7 (0.9)	0.70
Systolic blood pressure on scene, mm Hg	125 (33)	129 (33)	0.36
Systolic blood pressure on hospital arrival, mm Hg	127 (27)	126 (22)	0.89
Pulse on scene, bpm	107 (21)	106 (28)	0.70
Pulse on hospital arrival, bpm	101 (25)	101 (23)	0.88
O ₂ saturation on scene	98 (96, 98)	98 (97, 99)	0.02
O ₂ saturation on hospital arrival	98 (97, 99)	99 (97, 99)	0.06
ETCO ₂ on scene	41.6 (12.7)	42.1 (11.2)	0.75
ETCO ₂ on hospital arrival	35.7 (6.0)	36.2 (8.8)	0.63
Cold fluid, mL	1900 (1000, 2000)	N/A	

ETCO₂ indicates end-tidal CO₂; and N/A, not applicable. Values are mean (SD) or median (interquartile range). *P calculated by *t* test or χ^2 test.

paramedic-cooled patients compared with 52.6% in the hospital-cooled patients, and this difference was not significant (risk ratio 0.90, 95% confidence interval 0.70 to 1.17, *P*=0.43).

In 1 secondary outcome measure, paramedic-cooled patients had a mean temperature on hospital arrival of 34.4°C (95% confidence interval 34.1°C to 34.6°C) compared with patients allocated to hospital cooling, who had a mean temperature of 35.2°C (95% confidence interval 34.9°C to

35.4°C). There were no differences in the other secondary outcome measures because no patient developed pulmonary edema during the infusion of cold fluid or recurrent cardiac arrest en route to the hospital.

Discussion

In this prospective, randomized controlled trial, paramedic induction of therapeutic hypothermia before hospital arrival decreased patient temperature compared with cooling after arrival but did not result in improved patient functional outcome at hospital discharge. The difference in patient temperature between the treatment group and the control group was modest (0.8°C) and of relatively short duration. We surmise that this relatively brief difference in core temperature was insufficient to have a measurable effect on patient outcomes at hospital discharge.

Therapeutic hypothermia is recommended for the treatment of anoxic neurological injury after resuscitation from OHCA when the initial cardiac rhythm is VF, based on the findings of 2 clinical trials. The first trial was conducted in Europe in comatose survivors of prehospital cardiac arrest and enrolled 273 patients, with 136 patients undergoing therapeutic hypothermia (33°C for 24 hours) and 137 patients maintained at normothermia.⁵ At 6 months, 55% of the cooled patients had good outcome compared with 39% of normothermic control subjects (risk ratio 1.4, 95% confidence interval 1.08 to 1.81). In this first trial, cooling was instituted with a cooled air mattress, and this resulted in very slow cooling, such that at 4 hours after randomization, there was only a 1°C difference between the groups.

The second study from Australia enrolled 77 patients who were resuscitated from OHCA with an initial cardiac rhythm of VF.⁶ At hospital discharge, 49% of patients who were cooled to 33°C for 12 hours had good outcome compared with 26% of the control group. After multivariate analysis for differences at baseline, the odds ratio for good outcome in the hypothermic group was 5.25 (95% confidence interval 1.47 to 18.76, *P*=0.011). The rate of cooling in this second study was also relatively slow, with a mean decrease in core temperature of 0.5°C per hour. Subsequent observational studies have confirmed that cooling for 12 to 24 hours after resuscitation improves outcomes after cardiac arrest when the initial cardiac rhythm is VF.^{15,16} Because there is compelling evidence from laboratory studies that earlier therapeutic hypothermia may improve outcomes still further, current research has focused on cooling techniques that may be applicable in the prehospital setting.

One feasible technique for patient cooling in the prehospital setting is a rapid infusion (>100 mL/min) of a large volume (40 mL/kg) of ice-cold intravenous crystalloid fluid (LVICF). After initial studies in the emergency department confirmed that this approach decreased core temperature without pulmonary edema,^{12,13} there has been preliminary experience with this approach in the prehospital setting.^{17,18}

Kim et al¹⁷ randomized 125 patients who had return of spontaneous circulation after resuscitation from OHCA to paramedic cooling with LVICF or normothermia. Of the 51 patients who had an initial cardiac rhythm of VF, 20 (69%) of 29 patients randomized to paramedic cooling recovered consciousness com-

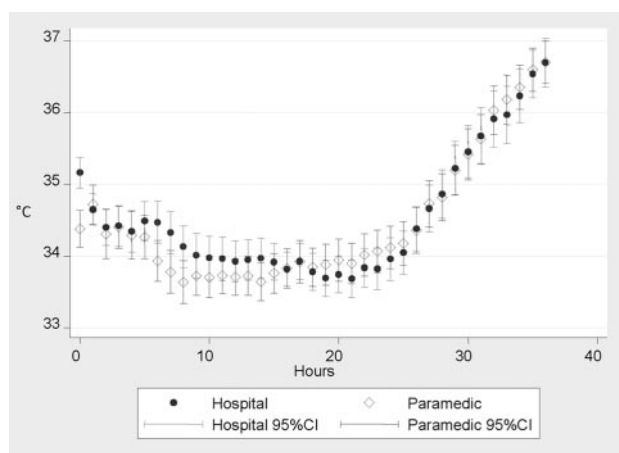


Figure 2. Temperatures of all patients. 95% CI indicates 95% confidence interval.

Table 3. Outcomes at Hospital Discharge

	Paramedic Cooling (n=118)	Hospital Cooling (n=116)	P*
Favorable outcome, n (%; 95% CI)	56 (47.5; 38.2–56.9)	61 (52.6; 43.1–61.9)	0.433
Discharge to home, n (%; 95% CI)	24 (20.3; 13.5–28.7)	34 (29.3; 21.2–38.5)	...
Discharge to rehabilitation, n (%; 95% CI)	32 (27.1; 19.3–36.1)	27 (23.3; 15.9–32.0)	...
Discharge to nursing home awake, n	0	0	...
Discharge to nursing home comatose, n (%; 95% CI)	0	1 (0.9; 0.02–4.7)	...
Dead, n (%; 95% CI)	62 (52.5; 43.1–61.8)	54 (46.6; 27.2–56.0)	...

CI indicates confidence interval.

*P calculated by χ^2 test.

pared with 10 (45%) of 22 VF patients randomized to normothermia ($P=0.15$). There were no differences between the groups in the rate of complications such as recurrent cardiac arrest or the development of pulmonary edema. In a second pilot study, Kämäräinen et al¹⁸ randomized 37 patients to either prehospital cooling (19 patients) or standard care (18 patients). At hospital arrival, the core temperature in the prehospital-cooled group was a mean of 34.1°C compared with 35.2°C in the treatment group. There were no significant differences between the groups in outcome.

Our larger study showed that although paramedic cooling resulted in a modest decrease in core temperature, there was no difference in outcomes at hospital discharge. The reasons for this finding are speculative. Of note, only half of the patients in the present study who were allocated to paramedic cooling received the full amount of LVICF because of the relatively short transport time to the hospital in a metropolitan setting. Consequently, there was a smaller decrease in the mean temperature of patients allocated to paramedic cooling and a smaller temperature difference between the groups on hospital arrival than we anticipated.

The present study has a number of limitations. First, it was not possible to blind treating paramedics and in-hospital medical staff to treatment allocation; however, the intensive care of post-cardiac arrest patients by attending medical staff followed standard guidelines, and it is unlikely that prehospital temperature management influenced major decisions by physicians after admission to the hospital. Second, measurement of tympanic temperature may be inferior to some other methods of measurement of core temperature, such as esophageal, bladder, or pulmonary artery temperature¹⁹; however, additional funding for the provision of equipment and training for esophageal temperature measurement was not available in our EMS. Also, the present study was terminated before the enrollment of the estimated required sample size. It is possible but extremely unlikely that a trend to improved outcomes in the paramedic-cooled patients would have emerged with larger study numbers. Another limitation of the present study is that 164 (41%) of 398 potentially eligible patients were not enrolled. It was not possible to accurately determine the reasons for nonenrollment of patients from the Victorian Ambulance Cardiac Arrest Register. On the other hand, because there was concealment of treatment allocation, it is unlikely that enrollment of these additional patients would have affected the results. Finally, it is possible that subtle improvements in neurological outcome may have been seen

with longer-term detailed neuropsychiatric assessment; however, this outcome measure requires considerable additional resources and was beyond the scope of the present study.

The present study has a number of strengths. Allocation of treatment was prospective, blinded, and computer randomized. The patients were well matched at enrollment, and there was a high rate of paramedic compliance with the study protocol. All patients were followed up until hospital discharge. In addition, the primary outcome measure of discharge direction to either home or rehabilitation is an objective measure of patient outcome.

Given that paramedics in the present study had already administered ≈ 1 L of ambient-temperature fluid during CPR, we would propose that future studies should examine the possible role of LVICF during CPR. It is possible that an infusion of ice-cold fluid during CPR would lead to earlier cerebral cooling and therefore improved outcomes. This approach has been tested in a number of laboratory studies. In 1 study, cooling during CPR resulted in an increase in the rate of successful defibrillation.²⁰ In a second study, the infusion of LVICF was shown to significantly decrease brain temperature.²¹ Preliminary clinical studies of cooling with LVICF during CPR have been reported recently, although patient numbers in these studies have been too small to demonstrate that this approach improves outcomes.^{22,23} Nevertheless, we would propose that future studies enroll patients during CPR to ascertain whether cooling during this phase is associated with improved outcomes.

In summary, we found that paramedics were able to effect a modest reduction in patient temperature during transport to hospital using a rapid infusion of LVICF; however, this decrease in core temperature was transient, and there was no measurable effect on patient outcomes compared with patients treated without active cooling. Future studies should examine the feasibility and efficacy of cooling commenced during CPR to assess whether this approach improves outcomes.

Appendix

Steering Committee: Stephen Bernard, MD, Peter Cameron, MD, Kevin Masci, D. Jamie Cooper, MD.

Statistician: Karen Smith, BSc, PhD.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The induction of therapeutic hypothermia after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest is recommended for the treatment of neurological injury by the American Heart Association; however, the optimal timing of this intervention is uncertain. Laboratory studies suggest that earlier cooling may improve neurological outcomes. This study reports the results of a randomized controlled trial in 234 patients comparing paramedic cooling after return of a circulation by use of a rapid infusion of large-volume, ice-cold intravenous fluid with cooling after hospital arrival. Paramedic cooling decreased core temperature by 0.8°C compared with patients allocated to hospital cooling, but the outcomes at hospital discharge were similar in both groups. Further research into cooling during cardiopulmonary resuscitation should be undertaken.

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