Effect of prehospital initiation of therapeutic hypothermia in adults with cardiac arrest on time-to-target temperature

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ABSTRACT

Objective: Despite growing adoption, the impact of prehospital initiation of therapeutic hypothermia on outcomes of cardiac arrest patients is unknown. The objective of this study was to determine if prehospital administration of cold intravenous fluids improved the time-to-target temperature.

Methods: All patients enrolled in an institutional post–cardiac arrest treatment pathway were prospectively registered into a quality assurance database. Patients undergoing cooling induction on hospital arrival were compared to those receiving a new treatment protocol initiated during the study period involving prehospital cooling with 4°C (39.2°F) normal saline. The primary outcome was the time-to-target temperature. Secondary outcomes included emergency medicine system transport time metrics, mortality, and neurologic status at discharge and 1 year.

Results: One hundred thirty-two patients were enrolled during the study period. The initial rhythm was ventricular fibrillation/tachycardia in 63% and asystole/pulseless electrical activity in 36%. Eighty patients received prehospital cooling and 52 patients did not and comprised the historical control group. Time-to-target temperatures were not significantly different between prehospital and hospital cooled groups (256 v. 271 minutes, respectively, $p = 0.64$), nor was there any improvement in hospital survival (54% v. 50%, $p = 0.67$), good neurologic outcome (49% v. 44%, $p = 0.61$), or 1-year survival (49% v. 42%, $p = 0.46$) between the two groups. Transport times were longer in the prehospital cooled group.

Conclusions: Out-of-hospital cardiac arrest patients treated with prehospital cooling before arrival at our urban hospital did not have faster time-to-target temperature or improvement in outcomes compared to patients cooled immediately on emergency department arrival. Further research is needed to determine if any benefits exist from prehospital cooling prior to its widespread adoption.

RÉSUMÉ

Objectif: Bien que l'amorce de l'hypothermie thérapeutique en phase préhospitalière soit de plus en plus répandue, on n'en connaît pas l'effet sur les résultats, chez les patients victimes d'un arrêt cardiaque. L'étude visait à déterminer si l'administration intraveineuse de liquides froids, en phase préhospitalière, permettait d'atteindre plus rapidement la température cible.

Méthode: Tous les patients soumis à un parcours de traitement, en établissement, pour un arrêt cardiaque ont été inscrits de manière prospective dans une base de données sur l'assurance de la qualité. Les patients soumis au refroidissement à leur arrivée à l'hôpital ont été comparés avec ceux soumis au nouveau protocole de traitement mis en œuvre durant la période à l'étude, comportant un refroidissement préhospitalier à l'aide de l'administration d'une solution physiologique salée maintenue à 4°C (39.2°F). Le principal critère d'évaluation était le temps nécessaire à l'atteinte de la température cible. Les critères d'évaluation secondaires comprenaient les mesures du temps de transport médical d'urgence, la mortalité, l'état neurologique au moment du congé et au bout de 1 an.

Résultats: Cent trente-deux patients ont été inscrits durant la période à l'étude. Les rythmes enregistrés au départ étaient la fibrillation ou la tachycardie ventriculaires dans 63% des cas ou encore l'asystole ou une activité électrique non pulsatile dans 36% des cas. Quatre-vingt patients ont été soumis au refroidissement préhospitalier et 52 patients, formant le groupe témoin historique, ne l'ont pas été. Le temps nécessaire à l'atteinte de la température cible n'était

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pas sensiblement différent entre le groupe de refroidissement préhospitalier et le groupe de refroidissement hospitalier (256 minutes contre [c.] 271, respectivement; $p = 0.64$), pas plus qu'il n'y avait d'amélioration en ce qui concerne la survie à l'hôpital (54% c. 50%; $p = 0.67$), l'état neurologique (49% c. 44%; $p = 0.61$) et la survie au bout de 1 an (49% c. 42%; $p = 0.46$) entre les deux groupes. Le temps de transport était toutefois plus long dans le groupe de refroidissement préhospitalier.

Conclusions: Le refroidissement préhospitalier chez les patients ayant subi un arrêt cardiaque, avant l'arrivée dans un hôpital urbain, n'a pas permis d'atteindre plus rapidement la température cible ou d'améliorer les résultats comparativement aux patients soumis au refroidissement dès leur arrivée au service des urgences. Aussi une recherche approfondie s'impose-t-elle afin de déterminer si le refroidissement préhospitalier comporte quelque avantage, et ce, avant l'adoption élargie de la pratique.

Keywords: cardiac arrest, prehospital medicine, therapeutic hypothermia

The Resuscitation Outcomes Consortium estimates that there are 359,000 out-of-hospital cardiac arrests (OOHCAs) in the United States each year.[1] Following two landmark studies in 2002, therapeutic hypothermia (TH) has become standard treatment for patients who remain comatose following return of spontaneous circulation (ROSC) after cardiac arrest.[2,3] Observational experiences have confirmed the feasibility of cooling, and there has been consensus across guidelines that cooling initiation following ROSC is beneficial to both mortality and neurologic outcomes.[4,5]

The optimal timing of therapeutic cooling remains unclear. Animal models have demonstrated that immediate and faster cooling yields improved outcomes,[6–8] but other studies have suggested that no benefit exists in short-term survival with rapid cooling, even when compared to normothermic postresuscitation care.[8] Observational human studies, although limited by their design, have also yielded conflicting results, with rapid cooling reported to be associated with improved, neutral, and negative effects on neurologic status and mortality.[9–15]

Despite the lack of clear evidence, many prehospital systems have implemented prehospital cooling protocols for post–cardiac arrest patients who remain comatose in the field. The benefit, if any, of this practice is unknown. The purpose of our study was to assess the impact of prehospital cooling on process measures and patient outcomes. Our primary objective was to determine if prehospital administration of cold intravenous (IV) fluids improved the time-to-target temperature. For secondary purposes, we analyzed the effect of prehospital cooling on mortality at hospital discharge and 1 year, neurologic outcome, and emergency medical system (EMS) time metrics.

METHODS

Study design and setting

We performed a retrospective analysis on all patients treated in the TH clinical pathway of Carolinas Medical Center, an urban, 900-bed teaching hospital, from November 2007 through November 2011. This was a before-and-after study, with the intervention being initiation of prehospital cooling, whereas the historical control group received no prehospital cooling. Our institution is a regional cardiac resuscitation centre that serves a network of 25 referring hospitals in the region and an ST elevation myocardial infarction (STEMI) receiving centre as designated by the American Heart Association Mission: Lifeline systems of care program. In April 2009 (approximately midway through our enrolment period), our local prehospital EMS agency implemented a protocol for prehospital cooling of patients experiencing OOHCA.

The EMS agency under study, Mecklenburg EMS Agency, is a municipal system serving a population of approximately 867,000. Over the study period, its average annual call volume was 90,000, resulting in approximately 69,000 patient transports. Patients were transported to any of the seven metropolitan hospitals of a single academic institution and a separate regional tertiary care facility. All ambulances were staffed with at least one paramedic and one emergency medical technician (EMT)-basic. First responders within the city and county were trained at the EMT-basic level and had access to an automated external defibrillator (AED). Prehospital triage, treatment, and transport protocols were uniform within both the county and the city limits.

Our protocol for prehospital cooling has been described previously.[16] Briefly, prehospital providers initiated infusion of cooled normal saline (4°C

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[39.2°F]) via the first established IV or intraosseous access for all nontraumatic cardiac arrest victims regardless of their initial rhythm. This included patients undergoing active resuscitation for cardiac arrest or following ROSC, with the goal of earliest possible initiation of cooling. Infusions were given as 500 mL rapid IV bolus aliquots by gravity infusion. Patients could receive repeated rounds of infusion up to a maximum of 2 L of fluid. Ambulances were equipped with refrigerators that maintained 1 L normal saline bags at 4°C. All other patient care was in accordance with Advanced Cardiac Life Support guidelines. Prehospital providers did not administer paralytics or sedatives and had instructions to discontinue TH if shivering developed.

Patients receiving prehospital TH served as the intervention group of this analysis and were compared to patients enrolled prior to the implementation of a prehospital cooling protocol. Our historical controls thus had initiation of TH in the emergency department (ED). The in-hospital cooling protocol was standardized for both the intervention and the control group, and there were no changes to the in-hospital protocol during the study period. This protocol included placement of ice packs to the groin, axilla, and neck; continuation of cooled IV fluid until a total of 30 mL/kg was administered; and implementation of the CR Bard (formerly Medivance, Inc., Louisville, CO) Arctic Sun 2000 cooling device set to achieve a target temperature of 33°C (91.4°F) as rapidly as possible.

This investigation was a retrospective analysis of an existing database. Clinical data, including arrest and treatment variables, complications, and outcomes, were prospectively collected on consecutive patients through the use of a preformatted standard data collection tool using Utstein criteria.[17] All data elements were chart abstracted and underwent both concurrent and retrospective review. These elements remained consistent throughout the study period and were defined using a "data dictionary." All data were manually entered from the electronic medical records and EMS records into a Web-based data collection tool. No interrater reliability assessment of the data elements was performed. The institutional review and privacy board of Carolinas Medical Center approved this study.

Study subjects

Patients experiencing a cardiac arrest of suspected cardiac etiology, regardless of presenting rhythm, received initiation of prehospital TH. Only those arriving directly at our centre via ground prehospital transport were eligible for study inclusion; patients transferred from outlying hospitals were excluded. Patients eligible for our hospital TH protocol were identified in the ED following arrival. Resuscitated victims of nontraumatic cardiac arrest with persistent coma (defined as a Glasgow Coma Scale [GCS] score $\leq$ 8 and/or unable to follow verbal commands) for at least 15 minutes following ROSC were eligible. The guideline emphasized the evidence for a benefit from therapeutic cooling in patients suffering cardiac arrest with an initial rhythm of ventricular tachycardia or ventricular fibrillation. However, all nontraumatic patients were eligible for the clinical pathway regardless of their initial arrest rhythm. Our guideline recommended strong consideration of cooling for patients suffering arrest with an initial rhythm of pulseless electrical activity or asystole if the time of arrest to ROSC was less than 30 minutes. Patients were included in the analysis if they survived to reach the intensive care unit (ICU) with intent to complete the cooling pathway. In the setting of arrests with an initial rhythm other than ventricular tachycardia or ventricular fibrillation, the decision to enrol into the cooling pathway was made after a joint discussion between the attending emergency physician and the critical care physician.

Absolute contraindications for pathway implementation included a valid do not resuscitate order or known severe terminal illness preceding the cardiac arrest. Relative contraindications included pregnancy, encephalopathy suspected to be unrelated to cerebral anoxia (e.g., overdose, intoxication, intracranial hemorrhage, stroke, or trauma), active hemorrhage, severe systemic infection, moribund cardiovascular status or severe shock refractory to medical interventions, arrest duration greater than 60 minutes, and arrest to cooling initiation interval greater than 6 hours. Clinical discretion was emphasized and superseded the relative contraindications if the perceived potential benefit of therapy outweighed the risk. Continuation of TH initiated in the prehospital setting was not mandatory and occurred at the discretion of treating physicians on arrival at our centre.

Data analysis

We designed our study to have 90% power to detect a 10% absolute difference in time-to-target temperature,

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Table 1. Participant characteristics

Characteristic	Total (*N* = 132)	Prehospital cooling (*n* = 80)	No prehospital cooling (*n* = 52)	*p* value
Age, mean years ± SD	58.2 ± 14.0	58.4 ± 12.8	57.8 ± 15.8	0.84
Male gender, *n* (%)	82 (62)	52 (65)	30 (58)	0.40
Witnessed arrest, *n* (%)	111 (84)	65 (81)	46 (89)	0.27
Bystander CPR, *n* (%)	94 (75)	65 (81)	29 (63)	0.02
Field AED use, *n* (%)	53 (40)	38 (48)	15 (29)	0.03
Time from arrest to ROSC* (min)	19 (12, 29)	20 (14, 27)	17 (8, 30)	0.14
Initial arrest rhythm, *n* (%)				
VT/VF	83 (63)	50 (63)	33 (64)	0.52
PEA	28 (21)	15 (19)	13 (25)	
Asystole	20 (15)	14 (18)	6 (12)	
Best GCS score prior to TH*	3 (3, 3)	3 (3, 3)	3 (3, 4)	0.47
STEMI at presentation	11 (8.3%)	6 (8%)	5 (10%)	0.75

AED = automated external defibrillator; CPR = cardiopulmonary resuscitation; GCS = Glasgow Coma Scale; PEA = pulseless electrical activity; STEMI=ST elevation myocardial infarction; TH = therapeutic hypothermia; VF = ventricular fibrillation; VT = ventricular tachycardia.
*Median and interquartile range provided.

based on the mean and standard deviation (SD) for the population under study. Our primary outcome was the time-to-target temperature following achievement of ROSC. Secondary outcomes were survival to hospital discharge, 1-year mortality, neurologic outcome as measured by the Pittsburgh Cerebral Performance Category,[17] and process of care measures focusing on transport times. Cerebral functional status was determined at hospital discharge, and Pittsburgh Cerebral Performance Category 1 or 2 was deemed to be a good neurologic outcome.[2] All patients admitted to the ICU with intention to undergo TH were included in the analysis, regardless of the extent to which the cooling protocol was followed or completed. Health care system electronic health records and the Social Security Death Index were queried to determine the survival of subjects at 1-year postarrest.

For the analysis, categorical variables were compared with the chi-square test or, in the case of small counts, Fisher exact tests. Two-sample *t*-tests and Wilcoxon rank sum tests were used for continuous variables as appropriate, based on the distribution of the data. Two-sided *p* values less than 0.05 were considered statistically significant. One-year survival was assessed using Kaplan-Meier estimates and a log-rank test. A secondary analysis was performed using an

Table 2. Process of care metrics

	Total (*N* = 132)	Prehospital cooling (*n* = 80)	No prehospital cooling (*n* = 52)	*p* value
Prehospital fluids initiated before ROSC, *n* (%)	59 (48)	57 (74)	2 (4)	< 0.001
Achievement of target temperature, *n* (%)	131 (99)	79 (99)	52 (100)	> 0.99
Time from arrest to hospital arrival*	40 (33, 49)	44 (37, 53)	34 (19, 41)	< 0.001
Time of initiation of cold fluids to hospital arrival*	15 (−13, 32)	30 (19, 38)	−22 (−75, −10)	< 0.001
Time of ROSC to hospital arrival*	18 (5, 30)	20 (13, 32)	12 (0, 23)	0.005
Time from EMS arrival to hospital arrival*	34 (26, 42)	38 (30, 43)	26 (22, 35)	< 0.001
Time from collapse to initiation of cooling*	26 (14, 59)	16 (11, 21)	66 (38, 110)	< 0.001
ROSC to target temperature*	257 (184, 349)	256 (185, 341)	271 (184, 369)	0.64

EMS = emergency medical service; ROSC = return of spontaneous circulation.
*Median and interquartile range in minutes.

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Table 3. Clinical outcomes

Outcome	Hospital survival (n = 69)	p value	Good neurologic outcome (n = 62)	p value
Prehospital cooling, n (%)	43 (54)	0.67	39 (49)	0.61
No prehospital cooling, n (%)	26 (50)		23 (44)	
Time of fluid initiation				
Initiated pre-ROSC (n = 59), n (%)	28 (48)	0.35	25 (42)	0.39
Initiated post-ROSC (n = 64), n (%)	36 (56)		32 (50)	

ROSC = return of spontaneous circulation.

unadjusted Cox proportional hazards model to determine if differences existed between the prehospital cooling and the in-hospital cooling groups. This study was not powered to detect a difference in mortality. All analyses were conducted using *SAS* statistical software version 9.2 (SAS Institute, Cary, NC).

RESULTS

One hundred thirty-two OOHCA patients were enrolled during the study period: 80 who received prehospital cooling and 52 who did not and had TH initiated in the ED. Baseline participant characteristics are shown in Table 1. Patients in the prehospital cooling group were more likely to have received bystander cardiopulmonary resuscitation (CPR) and field AED use.

Process of care metrics for the two groups are provided in Table 2. Of those who were administered cold IV fluids prehospital, 31% received < 500 mL, 46% received 500 to 1,000 mL, 12% received 1,001 to 1,500 mL, and 11% received 1,501 to 2,000 mL. There was no difference in time-to-target temperature between the groups receiving and not receiving prehospital cooling (256 [95% CI 185–341] and 271 [95% CI 184–369] minutes, respectively, p = 0.64). Transport intervals for patients receiving prehospital TH were all longer than those receiving prehospital TH. In contrast, time from collapse to initiation of cooling was longer in patients cooled on hospital arrival compared to those cooled prehospital.

Clinical outcomes are provided in Table 3. There was no statistically significant difference found in hospital survival or good neurologic outcomes in the two groups. A subgroup comparison of the patients who received initiation of cold IV fluids prior to ROSC (i.e., intra-arrest initiation) with those who received initiation following ROSC similarly found no significant difference in clinical outcomes.

Figure 1 provides data for survival at 1 year and shows that there was no statistically significant difference between the groups. Data were available for 128 patients; the 4 censored patients were alive but had not reached the 1-year threshold at the time of the analysis.

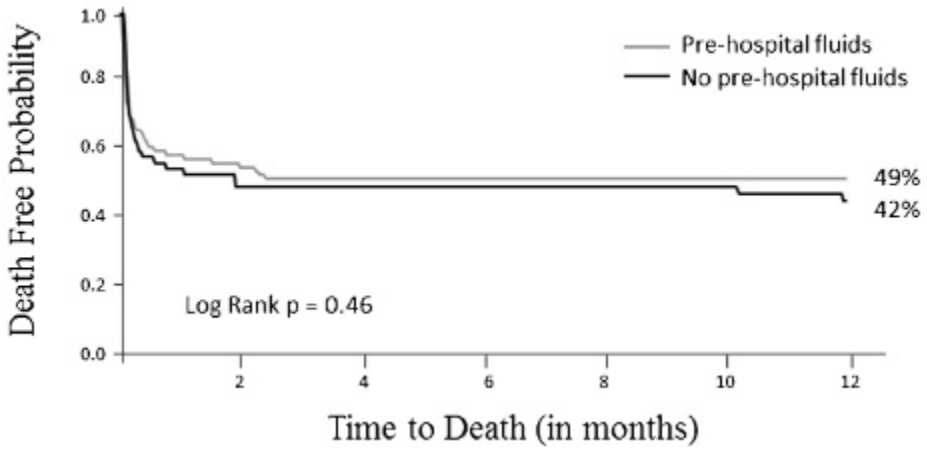

Figure 1. One-year mortality.

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DISCUSSION

Our results suggest that prehospital implementation of therapeutic cooling expedites TH induction but is not associated with improved time-to-target temperature and results in prehospital transport delays. Our study adds to the evidence on prehospital cooling by suggesting that simply implementing the earliest possible postarrest cooling regimen, via intra-arrest cooling or immediately postarrest, does not necessarily result in achievement of a faster time-to-goal temperature.

Post–cardiac arrest TH is a powerful treatment that is known to impact survival and neurologic outcome and has been widely emphasized over the past decade. The optimal method, timing, rate, and period of TH are unclear and represent a prime target of investigation to improve therapeutic effect.

Although our findings may arise from the inherent challenges of cooling in the prehospital environment, it is noteworthy that we also found a longer period of prehospital care among those patients who received prehospital cooling. We suspect that a contributor to the prolonged EMS intervals we observed was the implementation of a prehospital "focused CPR" protocol several months prior to initiation of the TH protocol. This protocol emphasized minimally interrupted chest compressions and remaining on the scene of an arrest for a minimum of 20 minutes or until ROSC was achieved. When this protocol is considered in the context of the increased bystander CPR and field AED use in patients who received prehospital cooling, it is possible that these interventions may have either contributed to the observed delayed time to hospital arrival or led to an increased propensity to continue the cooling protocol in-hospital once such patients arrived. Previous research suggests that the delay this protocol resulted in may not have any bearing on survival outcomes.[18,19] It is clear that early initiation of cooling is not the sole factor in achieving goal temperature and possible that delays arising from patient sedation, paralysis, deviation from hospital protocol, and additional TH induction measures impacted our results. Our centre's post–cardiac arrest clinical pathway is composed of a bundle of therapeutic interventions in addition to TH. The prehospital delays present in our intervention group may be a surrogate for delays in other important hospital-based interventions, including cardiopulmonary stabilization and percutaneous coronary intervention.

Despite the lack of benefit in terms of time-to-target temperature, survival, and neurologic outcome, in our study population, our findings do not completely exclude the possibility of benefit from prehospital cooling. Although not studied, the initiation of prehospital cooling could prevent hyperthermia despite not leading to a faster time-to-target temperature, which could be protective to the injured brain. The therapeutic momentum of initiating cooling in the field could also lead to increased overall completion of the entire therapeutic cooling pathway and more aggressive overall care. The determination of whether prehospital cooling offers benefit requires further assessment investigating a variety of parameters.

Data on the impact of early TH are confusing and conflicted. Animal studies have suggested that early cooling improves ROSC and outcomes.[6,8] Based on the premise of time sensitivity of cooling for neuroprotection, many EMS systems have adopted prehospital TH induction to expedite cooling. Prehospital induction via 4°C normal saline is feasible, safe, and effective in decreasing core temperature.[11,13] However, four prospective randomized trials have found no difference in outcomes with prehospital cooling initiation.[12,14,20,21] In contrast, a retrospective study using ice packs found deleterious effects of every 5-minute delay in TH initiation and every 30-minute delay in time-to-target temperature.[22] Rapid cooling has been associated with adverse outcomes thought to be linked to more severely impaired thermoregulation in those with severe brain injury.[10,23] Adjustment for admission body temperature appears to negate the signal arising from analyses of this issue.[18,20] Garrett and colleagues suggested potential improved ROSC rates when intra-arrest cooling was used.[23] Taken in its entirety, the body of literature regarding the optimal timing of TH induction remains unclear. Our study adds to the current literature by demonstrating that prehospital cooling with IV fluids does not shorten the time-to-target temperature.

LIMITATIONS

A number of important limitations should be considered when interpreting the results of our study. Our small sample size limited our ability to discriminate between small but potentially important outcome differences. Although none of the differences we found in clinical outcomes were statistically significant, this may have arisen because of insufficient power to detect

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this level of differences. In addition, the potential exists for unrecognized bias given our nonrandomized design, inclusion of nonshockable rhythms being subject to the discretion of the treating physician, and the possibility of unrecognized factors or confounders associated with patient management and outcome. Our study was performed in an urban metropolitan centre with relatively short transport times; thus, our results may not be generalizable to regions with longer transport times.

The focus of our prehospital TH intervention on cold IV fluid induction and more aggressive measures to achieve early prehospital cooling may have impacted patients differently as some have suggested that IV fluids may not remain adequately chilled in warm environments.[19,24,25] Our prehospital providers were not equipped with thermometers, and the first recorded temperature on study patients was on hospital arrival. Many of the sicker patients may have experienced autonomic dysregulation, which could have affected their cooling rates. Another consideration was that our prehospital providers' protocol for shivering included discontinuation of TH until arrival at the hospital. We were unable to determine how many patients had their prehospital cooling halted in this manner.

Our study population included those selected as good candidates for TH in our institutional clinical pathway rather than all patients initially resuscitated from OOHCA. The potential for therapeutic momentum via prehospital initiation of cooling may have led to increased patients entering the clinical pathway. This method is generalizable as accrual is more reflective of clinical medicine outside the research setting. We are confident that there was no bias on the part of the prehospital providers in terms of cooling initiation because regardless of ROSC, all patients with OOHCA had prehospital cooling initiated. They were included in the study, following our intention-to-treat analysis, only if they survived to ICU admission with the intention to undergo cooling, regardless of the degree to which the protocol was completed. The initiation of a focused CPR protocol during the study period, with a de-emphasis on airway and focus on minimally interrupted chest compressions, may also have affected our findings.

CONCLUSIONS

OOHCA patients treated with prehospital cooling before arrival at our urban hospital did not have a faster time-to-target temperature or improvement in outcomes compared to patients cooled immediately on ED arrival. Notably, the patients receiving prehospital TH did experience longer transport times, including arrest-to-ED, ROSC-to-ED, and EMS-arrival-to-ED times. Further research is needed to determine if any benefits exist from prehospital cooling prior to its widespread adoption.

Competing interests: None declared.

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