Temperature Control Parameters Are Important: Earlier Preinduction Is Associated With Improved Outcomes Following Out-of-Hospital Cardiac Arrest

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Study objective: Temperature control trials in cardiac arrest patients have not reliably conferred neuroprotective benefit but have been limited by inconsistent treatment parameters. To evaluate the presence of a time dependent treatment effect, we assessed the association between preinduction time and clinical outcomes.

Methods: In this retrospective, single academic center study between 2014 and 2022, consecutive out-of-hospital cardiac arrest (OHCA) patients treated with temperature control were identified. Preinduction was defined as the time from hospital arrival to initiation of a closed-loop temperature feedback device [door to temperature control initiation time], and early door to temperature control device time was defined a priori as <3 hours. We assessed the association between good neurologic outcome (cerebral performance category 1 to 2) and door to temperature control device time using logistic regression. The proportion of patients who survived to hospital discharge was evaluated as a secondary outcome. A sensitivity analysis using inverse probability treatment weighting, created using a propensity score, was performed to minimize measurable confounding.

Results: Three hundred and forty-seven OHCA patients were included; the early door to temperature control device cohort included 75 (21.6%) patients with a median (interquartile range) door to temperature control device time of 2.50 (2.03 to 2.75) hours, whereas the late door to temperature control device cohort included 272 (78.4%) patients with a median (interquartile range) door to temperature control device time of 5.18 (4.19 to 6.41) hours. In the multivariable logistic regression model, early door to temperature control device time was associated with improved good neurologic outcome and survival before [adjusted odds ratio (OR) (95% confidence interval) 2.36 (1.16 to 4.81) and 3.02 (1.54 to 6.02)] and after [adjusted OR (95% confidence interval) 1.95 (1.19 to 3.79) and 2.14 (1.33 to 3.36)] inverse probability of treatment weighting, respectively.

Conclusion: In our study of OHCA patients, a shorter preinduction time for temperature control was associated with improved good neurologic outcome and survival. This finding may indicate that early initiation in the emergency department will confer benefit. Our findings are hypothesis generating and need to be validated in future prospective trials. [Ann Emerg Med. 2024;84:549-559.]

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INTRODUCTION

Background

Hypoxic ischemic brain injury is the leading cause of death and disability following out-of-hospital cardiac arrest (OHCA).[1] The robust neuroprotective effects of induced hypothermia in preclinical models of hypoxic ischemic brain injury have inconsistently translated into clinical trials and practice.[2] Failure to tightly control temperature control parameters, such as time to initiation, may contribute to falsely neutral trial results.

High-quality temperature control includes rapid initiation of cooling and adjunctive treatments to reduce shivering thermogenesis.[3] To date, trials have not accounted for high-quality temperature control parameters, such as time to initiation (preinduction), pharmacologic interventions for shivering, and device selection.[4,5] In a post hoc analysis of the Continuous Chest Compressions trial, rapid initiation of temperature control (<122 minutes from hospital arrival) was associated with improved survival to hospital discharge.[6] Multidisciplinary quality

Editor's Capsule Summary

What is already known on this topic

Delays in initiation of targeted temperature management after cardiac arrest may reduce the treatment effect of targeted temperature management.

What question this study addressed

This hypothesis-generating study examined whether time to initiating targeted temperature management (> or <3 hours after arrest) was associated with outcome.

What this study adds to our knowledge

Among 347 out-of-hospital cardiac arrest patients, 75 had initiation of targeted temperature management <3 hours, which was associated with increased odds of survival (adjusted OR 3.02, 95% CI 1.54 to 6.02) and good neurological outcome (adjusted OR 2.36, 95% CI 1.16 to 4.81).

How this is relevant to clinical practice

When using targeted temperature management after cardiac arrest, consider rapid initiation within 3 hours of arrest.

improvement processes can reduce preinduction time and may contribute to improvements in survival and favorable neurologic outcome.[7,8] Shorter preinduction times in the emergency department are feasible, but it remains unclear whether they provide improved neuroprotection.[9]

Importance

Patients with a lower body temperature following return of spontaneous circulation (ROSC; spontaneous hypothermia) and those with a shorter (rapid) induction have worse neurologic outcomes.[10-13] Shivering thermogenesis during hypothermia induction is associated with improved neurologic outcomes but may result in delay to achieve target temperature.[13] Published clinical trials have focused on time to achieve target temperature, which includes both the preinduction (time to initiate cooling) and induction (rate of cooling) rates. Target temperature may be achieved rapidly due to treatment parameters (high-quality temperature control) or patient-related variables (lack of shivering thermogenesis). We believe that the preinduction time must be decoupled from time to achieve target temperature, as the inability to separate these may result in failure to detect a significant treatment benefit.[14]

Goals of This Investigation

We aimed to assess the effect of preinduction time on clinical outcomes after OHCA in patients treated with temperature control.

METHODS

Study Design and Settings

We conducted a retrospective review of a continuously collected OHCA cohort at a single academic medical center between January 1, 2014, and December 31, 2022. The decision to treat with temperature control was made by the consulting neurology team in collaboration with the emergency department, based on hospital protocols, and conducted using a closed-loop temperature feedback device. At our institution, a "chill alert" is called for all patients who achieve ROSC in the emergency department. This alert brings neurology and cardiology to the bedside for decisions regarding triage, temperature control, and brain-centered resuscitation. Our institutional temperature control protocol is an intensive care unit policy that dictates target temperature and duration of cooling but does not specify time to initiation or best practices to implement high-quality temperature control.[3] In the fall of 2021, coinciding with participation in the Influence of Cooling duration on Efficacy in Cardiac Arrest Patients (ICECAP; NCT04217551) trial, we started initiating temperature control with a closed-loop temperature feedback device in the emergency department. The goal core temperature for each patient was based on institutional protocols (33 °C to 36°C) or set to 33°C for patients eligible for the ICECAP trial, as above. While awaiting connection to a closed-loop temperature feedback device, patients were covered with icepacks or treated with cold saline solution (if volume resuscitation was required). We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology criteria for observational studies.

Selection of Participants

Cardiac arrest patients were identified using International Classification of Disease, Ninth Revision (427.5) and International Classification of Disease, Tenth Revision (I46.9) codes, followed by manual chart review to verify cardiac arrest occurrence and extract clinical data. Inclusion criteria were OHCA, age ≥18 years, treatment with temperature control, and admission to an intensive care unit after ROSC.[15] Given that early withdrawal of life-sustaining therapy leads to mortality in those who might have otherwise had a good functional outcome, we excluded patients with early withdrawal of life-sustaining therapy, defined as within 72 hours of cardiac arrest.[16,17]

An additional 3 patients were excluded for early discontinuation of temperature control prior to achieving temperature target (Figure E1, available at http://www.annemergmed.com). This study was approved by the Yale University Institutional Review Board (HIC 1506016080).

Intervention

We defined preinduction as time from hospital arrival to initiation of a closed-loop temperature feedback device [door to temperature control device] using either the Arctic Sun™ surface cooling (N=339, 98%) or ZOLL intravascular temperature management (N=8, 2%). Early door to temperature control device time was defined a priori as <3 hours. Three hours was selected as prior publications suggest benefit of initiating or achieving temperature control within 3 to 4 hours from ROSC.[18,19] In our cohort, it was not feasible to select a shorter duration target given the few patients with initiation of temperature control in ≤2 hours. The distribution of early or late door to temperature control device time by year can be found in the Figure E2, available at http://www.annemergmed.com.

Measurements

Data were extracted in a standardized and systematic fashion from the electronic medical record by the Yale joint data analytics team and by research associates (NK, CN, and EK) and a resident investigator (GM) under the direct supervision of faculty investigators (RB and EG) with internal procedures to ensure abstraction accuracy. Variables extracted from the electronic health record included: demographics, medical history, details of the arrest (location of arrest, witnessed arrest, bystander cardiopulmonary resuscitation [CPR], initial nonperfusing rhythm, time of the arrest, and time of ROSC), postarrest variables (initial core temperature, temperature control use, time of hospital arrival, time temperature control was initiated, time target temperature was achieved, initial lactate, initial pH, partial pressure of oxygen (PaO_2), FiO_2, vasopressor doses, withdrawal of life-sustaining therapy, and time from cardiac arrest to withdrawal of life-sustaining therapy), and clinical outcomes. If a variable was not documented, it was entered as not available. Age-adjusted Charlson Comorbidity Index was used to classify premorbid medical status.[20] Pittsburgh Cardiac Arrest Category was used to characterize postcardiac arrest syndrome severity.[21] In all patients, we assessed the mean arterial pressure (MAP), peak simultaneous vasopressor dose in norepinephrine equivalents, and rate of lactate clearance in mmol/hour over the first 24 hours from cardiac arrest.[22] We also calculated mean PaO_2 and partial pressure of carbon dioxide ($PaCO_2$) levels within the first 6 hours from cardiac arrest. These variables were used to assess whether postresuscitation care differed between the early and late cohort.

Outcomes

The primary outcome measure was good neurologic outcome at hospital discharge, defined by cerebral performance category of 1 or 2. Cerebral performance category at hospital discharge correlates well with long-term prognosis.[23,24] The cerebral performance category scores were determined by a single reviewer (RB, a neurointensivist) blinded to door to temperature control device using retrospective chart review of physical, occupational, and speech therapy notes at the time of hospital discharge. Cerebral performance category 3 is a broad category that includes the spectrum of patients who are awake and communicative but dependent in activities of daily living to those with significant cognitive impairment. We defined poor neurologic outcome as cerebral performance category 3 to 5 but captured the ability to follow commands at hospital discharge in patients with a cerebral performance category 3.[25] The secondary outcome measure was survival to hospital discharge.

Analysis

Categoric variables were reported as counts (percentages), normal continuous variables as means (SD), and ordinal and nonnormal continuous variables as medians [interquartile range (IQR)]. Normal continuous variables were compared between groups using a t test. Categoric variables were compared using chi-squared test with continuity correction. Ordinal or nonnormal continuous variables were compared using Wilcoxon rank-sum test. Missing values were labeled as NA. For the primary analysis there was only one missing value (one patient who did not have an initial lactate level was included in the primary analysis but excluded from the sensitivity analysis). There were 22 patients with missing values for MAP (n=1), peak norepinephrine equivalents (n=0), lactate clearance (n=14), PaO_2 (n=10), or $PaCO_2$ (n=5) (Table E1 available at http://www.annemergmed.com). Standardized mean difference (SMD) was used to quantify the difference between groups. A SMD of 0.2, 0.5, and ≥0.8 were considered small, medium, and large effect sizes, respectively.

We performed univariable and multivariable logistic regression analyses to assess the association between continuous door to temperature control device time and outcomes. We repeated the above analyses comparing

outcomes between the early and late door to temperature control device time cohorts, which was defined based on a threshold of 3 hours. In the multivariable models, we adjusted for age, sex, age-adjusted Charlson Comorbidity Index, initial rhythm, bystander CPR, witnessed, initial core temperature, initial lactate level, and Pittsburgh Cardiac Arrest Category, all known independent predictors of neurologic outcome.[26] Many of these variables were predictors of the primary outcome in our univariable analysis (Table E2, available at http://www.annemergmed.com).

To reduce the effects of measurable confounding between the early and late door to temperature control device cohorts, we used inverse probability of treatment weighting to construct a balanced pseudopopulation. The propensity score model included the following covariates: age, sex, Charlson Comorbidity Index, initial rhythm, bystander CPR, witnessed, Pittsburgh Cardiac Arrest Category, initial lactate level, initial core temperature, and year of cardiac arrest. Target temperature was determined to be a downstream effect or collider as the exposure to early door to temperature control device time influenced choice of target temperature and strong predictors of outcome, such as Pittsburgh Cardiac Arrest Category and initial core temperature, influenced selection of target temperature.[27,28] Furthermore, target temperature was selected and achieved after treatment with temperature control was initiated. SMDs were estimated in the unweighted and weighted populations to ensure sufficient postweighting balance between cohorts for all potential confounders. Each patient was weighted by the inverse of the propensity score, and the average treatment effect on outcomes was computed using weighted logistic regression with bootstrap variance estimates using 50 random samples.[29] The same analyses were performed in each target temperature group to prove the robustness of the conclusions. Analyses were performed using R version 4.3.1.[30]

RESULTS

Characteristics of Study Subjects

Of 549 OHCA patients, 145 (26.4%) were excluded as they were not deemed eligible for treatment with temperature control. Per hospital policy, temperature control was not offered to patients who were following commands, hemodynamically unstable, or with life threatening hemorrhage (Table E3, available at http://www.annemergmed.com). Of the 404 (73.6%) patients treated with temperature control with a closed-loop temperature feedback device, 54 (13.3%) were excluded due to early withdrawal of life-sustaining therapy (5 in the early door to temperature control device time cohort, 49 in the late door to temperature control device cohort), and 3 (0.9%) were excluded due to discontinuation of temperature control prior to achieving target temperature (all in late door to temperature control device cohort), resulting in a cohort of 347 patients (Figure E1). Included patients were predominantly men (N=218, 62.8%), White (N=224, 64.6%), and had a mean (SD) age of 56.9 (16.2) years. The majority suffered a nonshockable rhythm arrest (N=233, 67.1%) and did not receive bystander CPR (N=192, 55.3%). The cohort had moderate to high postcardiac arrest syndrome severity with a median [IQR] Pittsburgh Cardiac Arrest Category score of 4 [3,4], mean (SD) initial lactate level of 9.1 (4.2) mmol/L, and mean (SD) initial pH of 7.28 (0.14).

There was a broad distribution of door to temperature control device time with a median [IQR] of 4.57 [3.19 to 5.98] hours (Figure 1). Seventy-five patients (21.6%) met criteria for early door to temperature control device time with a median [IQR] door to temperature control device time of 2.50 [2.03, 2.75] hours, and 272 (78.4%) met criteria for late door to temperature control device time with a median [IQR] of 5.18 [4.19 to 6.41] hours. Demographics, details of the arrest, illness severity, and postresuscitation management were similar between early and late door to temperature control device cohorts (Table 1). Although time from cardiac arrest to hospital arrival was similar between early and late door to temperature control device cohorts (0.6 [0.4 to 1.0] versus 0.5 [0.3 to 0.8] hours, SMD 0.32), there was a moderate group difference in time from cardiac arrest to target temperature, which was achieved faster in the early door to temperature control device cohort (4.9 [4.0 to 7.8] versus 8.7 [7.0 to 10.5] hours, SMD = 0.71).

Main Results

There was a linear association between door to temperature control device and log-odds of good neurologic outcome, with decreasing odds of good neurologic outcome as door to temperature control device increased (Figure 2). After adjustment for confounders, each hour delay in door to temperature control device was associated with a 20% (6% to 33%) decrease in odds of good neurologic outcome and a 16% (4% to 27%) decrease in odds of survival [adjusted OR (95% CI) 0.80 (0.67 to 0.94) and 0.84 (0.73 to 0.96), respectively]. Early door to temperature control device was associated with improved good neurologic outcome and survival with an adjusted OR (95% confidence interval) of 2.36 (1.16 to 4.81) and 3.02 (1.54 to 6.02), respectively (Table E4, available at http://www.annemergmed.com). Among

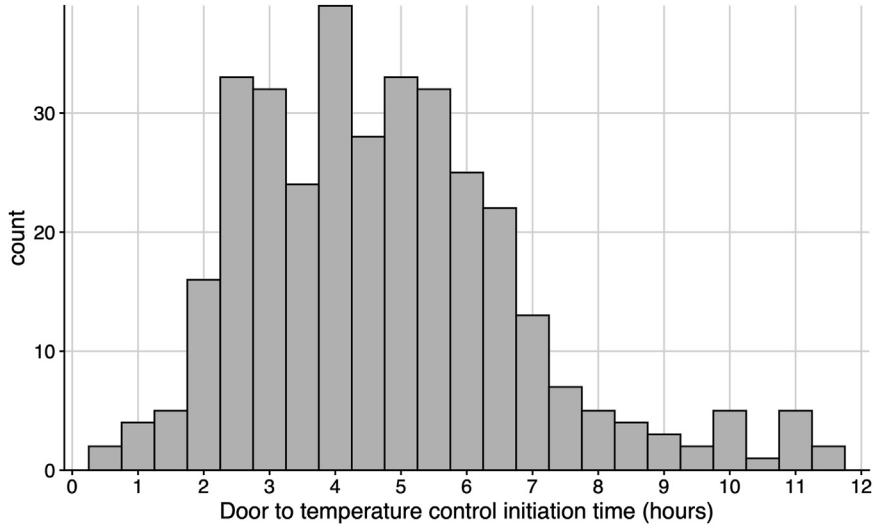

Figure 1. Distribution of preinduction time across the entire cohort (median [interquartile range] 4.57 [3.19 to 5.98] hours).

patients with cerebral performance category 3 at hospital discharge, 8 (10.7%) in the early door to temperature control device cohort versus 11 (4.0%) in the late door to temperature control device time cohort were following commands (SMD = 0.07). There was no significant association between time to achieve target temperature and outcomes (Table E5, available at http://www.annemergmed.com).

Postresuscitation care was assessed by evaluating hemodynamic, laboratory, and ventilator parameters. The cohort was adequately resuscitated with a mean (SD) MAP of 87.7 (11.7) mm Hg, PaO_2 of 133.9 (90.1) mm Hg, and $PaCO_2$ of 55.5 (18.3) mm Hg. Differences in MAP, peak NEE, rate of lactate clearance, PaO_2, and $PaCO_2$ between those with early versus late door to temperature control device had a small effect size (Table E1).

Table 1. Demographics, arrest-related details, postarrest management, illness severity, and outcomes for cohort, stratified by door to temperature control.

Variables	Late DTC (N=272)	Early DTC (N=75)	SMD
Age (y), mean (SD)	57.5 (16.0)	54.9 (17.0)	−0.16
Man, N (%)	163 (59.9)	55 (73.3)	0.14
White, N (%)	175 (64.3)	49 (65.3)	0.01
CCI, median [IQR]	2 [1-5]	2 [1-4]	−0.14
Shockable initial rhythm, N (%)	82 (30.1)	32 (42.7)	0.13
Bystander CPR, N (%)	117 (43.0)	38 (50.7)	0.07
Witnessed, N (%)	177 (65.1)	44 (58.7)	−0.06
Year of arrest, median [IQR]	2018 [2016-2020]	2021 [2017-2022]	0.39
PCAC, median [IQR]	4 [3-4]	4 [2-4]	−0.18
Initial lactate level*, mean (SD)	9.3 (4.3)	8.5 (4.0)	−0.20
Initial pH, mean (SD)	7.29 (0.15)	7.27 (0.14)	−0.14
Initial core temperature (°C), mean (SD)	35.6 (1.2)	35.6 (1.1)	0.05
Cardiac catheterization, N (%)	47 (17.3)	21 (28.0)	0.11
Percutaneous coronary intervention, N (%)	22 (8.1%)	6 (8.0%)	0.00
CA to hospital arrival (hours), median [IQR]	0.5 [0.3-0.8]	0.6 [0.4-1.0]	0.32
CA to target temperature (hours), median [IQR]	8.7 [7.0-10.5]	4.9 [4.0-7.8]	−0.71
Door to temperature control (hours), median [IQR]	5.2 [4.2-6.4]	2.5 [2.0-2.8]	−2.01
Target temperature <36 (°C), N (%)	154 (56.6)	53 (70.7)	0.14

CA, cardiac arrest; *CCI*, Charlson Comorbidity Index; *DTC*, door to temperature control; *IQR*, interquartile range; *PCAC*, Pittsburgh Cardiac Arrest Category.
*One missing value for initial lactate (N=1, 0.3%).

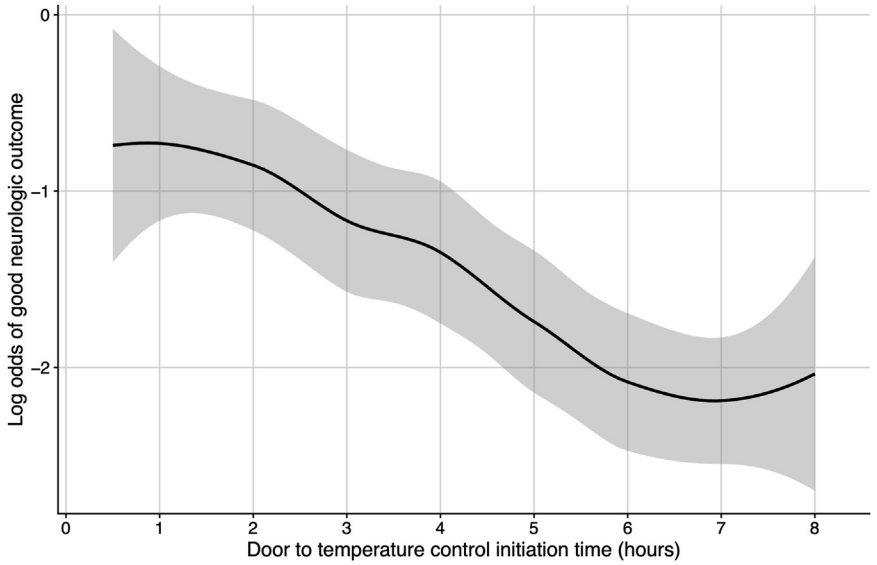

Figure 2. Log-odds of good neurologic outcome as a function of preinduction time. The odds of good neurologic outcome decreases with increasing preinduction time.

Sensitivity Analysis: Inverse Probability of Treatment Weighting

In the inverse probability of treatment weighting analysis, 1 patient was excluded due to missing initial lactate, leaving a total of 346 patients. After inverse probability of treatment weighting, all key baseline characteristics and covariates were well balanced (Figure 3, Table 2). A significantly greater proportion of patients achieved good neurologic outcome in the early door to temperature control device (28.0%) versus late door to temperature control device (15.5%) cohorts [OR (95% CI), 1.95 (1.19 to 3.79)] (Figure 4). Early door to

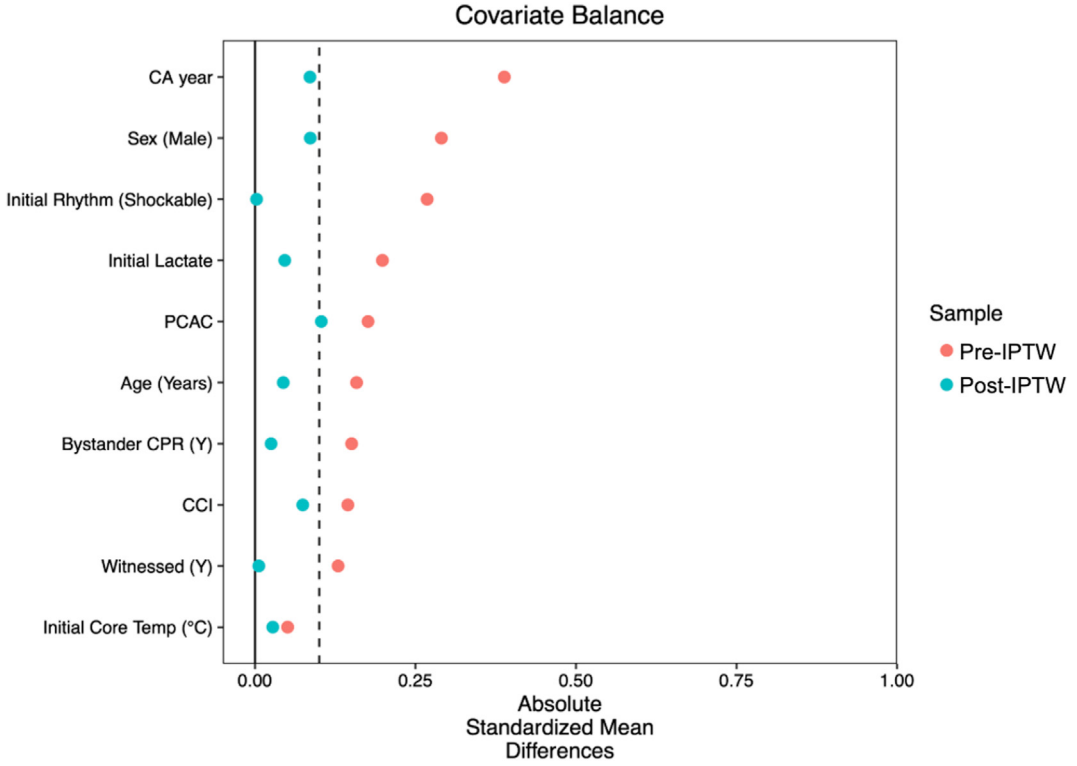

Figure 3. Covariate balance before and after inverse probability treatment weighting. Standard mean difference of $\leq$0.1 was considered balanced. The dotted line reflects a standard mean difference of 0.1. *CA*, cardiac arrest; *CCI*, Charlson Comorbidity Index; *CPR*, cardiopulmonary resuscitation; *IPTW*, Inverse probability treatment weighting; *PCAC*, Pittsburgh Cardiac Arrest Category.

Table 2. Demographics, arrest-related details, postarrest management, illness severity, stratified by door to temperature control following inverse probability of treatment weighting.

Variables	Late DTC	Early DTC	SMD
Age (y), mean (SD)	56.9 (16.0)	56.1 (17.3)	−0.04
Man (%)	63%	67%	0.09
CCI, mean (SD)	3.0 (2.8)	2.8 (2.4)	−0.08
Shockable initial rhythm (%)	32%	33%	0.00
Bystander CPR (%)	45%	46%	0.03
Witnessed (%)	64%	63%	−0.01
Year of arrest, mean (SD)	2018 (2.3)	2018 (2.9)	−0.09
PCAC, mean (SD)	3.4 (0.9)	3.3 (0.9)	−0.10
Initial lactate level (mmol/L), mean (SD)	9.1 (4.2)	8.9 (4.1)	−0.05
Initial core temperature (°C), mean (SD)	35.6 (1.2)	35.6 (1.2)	0.03

temperature control device time was also associated with higher proportion of survival to hospital discharge [OR (95% CI), 2.14 (1.33 to 3.36)]. A subgroup analysis was performed using the pseudopopulation to ensure that the relationship between door to temperature control device time, and outcomes were comparable by target temperature (Figure E3, available at http://www.annemergmed.com).

LIMITATIONS

There are several limitations of our study. The influence of high-quality temperature control, including time to temperature control initiation, is best answered using a prospective trial design. This is a single-center, retrospective study, which was only possible due to changes in practice (initiation of temperature control in the emergency department). With participation of the ICECAP trial, our site implemented policies and procedures to reduce door to temperature control device; this may have contributed to selection bias for which we could not control. Despite efforts to initiate temperature control in the emergency department, this was challenging, and we had few patients with early initiation of temperature control. We performed a sensitivity analysis using inverse probability of treatment

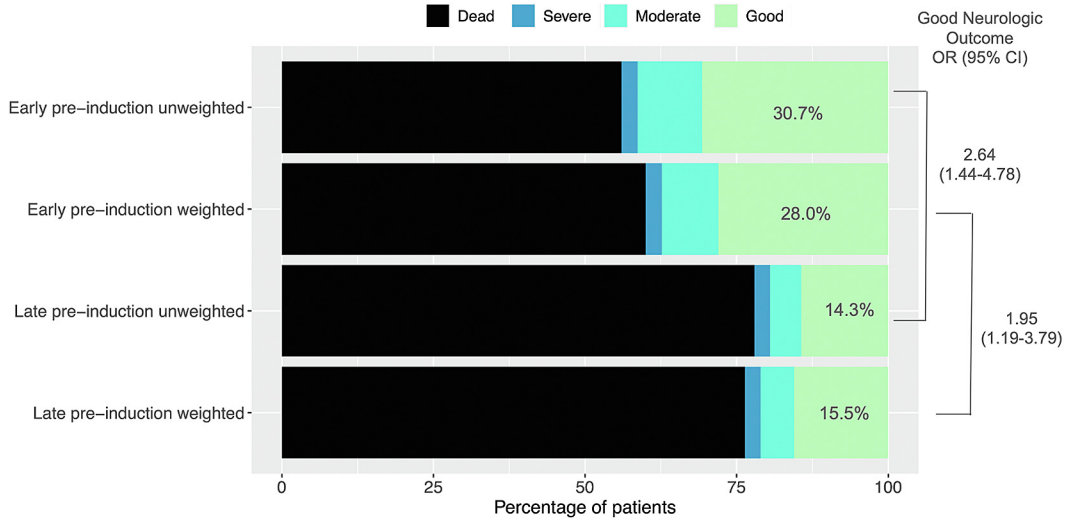

Figure 4. Distribution (%) of cerebral performance category scores at discharge among early preinduction unweighted, early preinduction weighted (postinverse probability of treatment weighting), late preinduction unweighted, and late preinduction weighted (post inverse probability of treatment weighting) cohorts. Cerebral performance category scores were listed as good (cerebral performance category 1 to 2), moderate (cerebral performance category 3), severe (cerebral performance category 4), and dead (cerebral performance category 5). Odds ratio (95% confidence interval [CI]) for good neurologic outcome are presented for early versus late preinduction unweighted and early versus late preinduction weighted (postinverse probability of treatment weighting).

weighting to minimize measurable confounding, but unmeasured confounding may still persist. Our results are hypothesis generating and should support a prospective trial evaluating the effect of temperature control implementation practices on efficacy for neuroprotection. Although it would be unethical to randomize patients to low-quality temperature control, we believe a prospective study can be performed using natural between-site variability in temperature control practices and quality improvement initiatives.

Although we excluded patients with early withdrawal of life-sustaining therapy from our analysis, we cannot eliminate the self-fulfilling prophecy bias, which has been a large contributor to confounding in many cardiac arrest studies. Prospective studies with standardized neuroprognostication protocols will be important to evaluate the effect of door to temperature control device time on clinical outcomes and minimize self-fulfilling prophecy bias. Although inter-rater reliability has previously been reported to be high, we had a single reviewer evaluating cerebral performance category scores, which may have introduced misclassification bias.[31] Lastly, a small number of patients were cooled with intravascular cooling (N=8), but our study is underpowered to understand the effect of method of cooling on outcomes.

Although we acknowledge these limitations, our study has important strengths. We present the largest study evaluating the association between preinduction time and neurologic outcomes. We acknowledge the complexity of temperature control and used the connection of a closed-loop temperature feedback device to constitute the start of controlled or high-quality temperature control. Our results are consistent with preclinical data, suggesting that time to treatment is critical and delays to initiation of temperature control may minimize its neuroprotective benefit.[14]

DISCUSSION

In our cohort, a shorter preinduction time was associated with improved survival and good neurologic outcome at hospital discharge. Even among patients with a cerebral performance category of 3 at hospital discharge, those in the early door to temperature control device cohort were more likely to follow commands. Our cohort does not reflect the population evaluated in the Targeted Temperature Management and Targeted Temperature Management-2 clinical trials and is composed predominantly of patients with a nonshockable rhythm arrest and high postcardiac arrest syndrome severity.[32,33] Our cohort has more similarities to the Targeted Temperature Management for Cardiac Arrest with Nonshockable Rhythm trial, which demonstrated a neuroprotective role of temperature control at 33°C compared to targeted normothermia.[34] The American Heart Association recently published a scientific advisory statement on temperature control advising caution when generalizing the findings of the Targeted Temperature Management-2 trial.[35]

High-quality preclinical data show a strong neuroprotective benefit of temperature control in cardiac arrest when hypothermia was induced immediately or within 60 minutes of ROSC.[2] In a Long Evans rat model of cardiac arrest, time to initiation of temperature control was indirectly correlated with survival and good neurologic outcome, with no neuroprotective or survival benefit found beyond 6 hours.[19] Although out-of-hospital cooling failed to show a neuroprotective benefit, a pooled analysis of two large pre-hospital trans-nasal evaporative intra-arrest cooling trials for OHCA (the PRINCE and PRINCESS trials), found that intra-arrest cooling was associated with a significant improvement in favorable neurologic outcomes in patients with a shockable rhythm [relative risk (95% CI) 1.43 (1.01 to 2.02)].[36] The methods used in out-of-hospital cooling may have also contributed to neutral results, with chilled saline solution resulting in higher rates of pulmonary edema and recurrent arrest.[37] Furthermore, these trials were limited by failure to control in-hospital cooling parameters, which may have influenced outcomes.[9,38]

A recent large, international multicenter randomized trial found no benefit of hypothermia to 33°C versus targeted normothermia; however, randomization occurred within 3 hours of ROSC and the median time from the start of intervention to a target of 34°C occurred after an additional 3 hours.[33] This population is not generalizable to the United States cardiac arrest population; postcardiac arrest syndrome severity, delayed preinduction, and the use of a pragmatic design without a standardized intervention may have contributed to the lack of benefit found for temperature control.

In a meta-analysis evaluating studies that deployed rapid versus slower cooling strategies, a nonlinear null relationship was identified between outcomes and time to target temperature beyond 4 hours, whereas a stepwise improvement in outcomes was identified when time to target temperature was less than 3 hours.[18] However, in a post hoc analysis of the Targeted Temperature Management-2 trial, the speed of cooling was not associated with neurologic outcome.[38] In this post hoc analysis, the average temperature at 4 hours following ROSC was used as a proxy of cooling speed and rapid cooling was more common in older patients and patients

with a lower temperature on admission, both associated with higher mortality.[38] As this trial looked at rate of induction, rather than preinduction, patient-related factors may have influenced the results. Our study is consistent with prior trials and suggests that a therapeutic window exists to maximize the neuroprotective benefit of temperature control.[6,19,39]

In our study, the group with rapid preinduction had a lower time to achieve target temperature; however, the median time remained above 4 hours. Although preinduction time was associated with outcomes, time to target temperature was not. We hypothesize that early initiation of a temperature control device proximal to ROSC, which both prevents fever but also lowers body temperature as reperfusion injury starts to develop, is of paramount importance. The time to achieve target temperature may also be important. However, we must understand the influence of patient selection and the quality of temperature control parameters to ascertain this.

We assessed differences in postresuscitation care between patients with early and late door to temperature control device times and found that both cohorts achieved reasonable hemodynamic, oxygenation, and ventilation parameters with no major differences between groups. Patients with early door to temperature control device times had numerically lower vasopressor requirements; this finding may be due to lower postcardiac arrest syndrome severity or the effects of early cooling-related vasoconstriction. Patients with early door to temperature control device had numerically lower mean $PaCO_2$, although the clinical significance of this is unknown.

Despite a decade of multiple, large, and resource-intensive temperature control trials, the level of evidence regarding temperature control remains low and prospective work to optimize temperature control parameters has been lacking.[40] In a post hoc analysis of the time-differentiated target temperature management after out-of-hospital cardiac arrest study, high-quality temperature control was provided to only 16% of OHCA participants.[4] Although the quality of temperature control was not associated with patient outcome, the sample size was insufficiently powered to detect this outcome. No clinical trial to date has been able to establish the therapeutic window for temperature control, and post hoc analyses are limited by a lack temperature control parameter standardization and neuroprognostication practices.[6,39]

Cardiac arrest survivors often remain in the emergency department during the golden hours after resuscitation when brain protective strategies to minimize secondary brain injury must be deployed. In 2 survey studies performed in France and Germany, temperature control was rarely initiated in the emergency department, with 80% to 85% of temperature control initiated in the intensive care unit.[41,42] Delay to intensive care unit admission, defined as emergency department boarding $\geq$ 6 hours, occurs in 1 in 4 OHCA patients and is associated with lower survival rate.[43,44] Quality improvement processes aimed at prioritizing aggressive interventions early in the emergency department can improve outcomes.[7,8]

We propose a paradigm shift focused on preinduction time rather than time to target temperature, which is confounded by patient-related factors and the severity of postcardiac arrest syndrome. In summary, the preinduction time of temperature control is modifiable and a reduction in the preinduction time may improve outcomes for OHCA patients. Emergency physicians have a critical role in acute resuscitation; systems of care can be standardized and may improve early treatment of comatose postcardiac arrest patients.

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Data sharing statement: The entire deidentified dataset, data dictionary and analytic code for this investigation are available upon request from the date of article publication by contacting Rachel Beekman at Rachel.Beekman@yale.edu.

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