Targeted Temperature Management Processes and Outcomes After Out-of-Hospital Cardiac Arrest: An Observational Cohort Study

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by the Physicians' Services Incorporated Foundation Resident Research Grant. The Toronto regional site of the Resuscitation Outcomes Consortium database is funded by the National Institutes of Health and the Canadian Institutes of Health Research, and the Strategies for Post Arrest Resuscitation Care network is funded by the Heart and Stroke Foundation of Canada and a Center Grant awarded to Rescu from the Laerdal Foundation.

Dr. Lin was supported by a Fellowship award from Canadian Institutes of Health Research (CIHR) and has received research funding from the Canadian Association of Emergency Physicians. He was also a worksheet author on the C2010 International Liaison Committee on Resuscitation (ILCOR) acute coronary syndrome taskforce and is currently an evidence reviewer on the C2015 ILCOR advanced life support taskforce. His institution received grant support from the Physicians' Services Incorporated Foundation (PSIF) and from the Canadian Association of Emergency Physicians (research grants). Dr. Scales was supported by a New Investigator award from CIHR and a Fellowship award from PSIF (Fellowship in Translational Health). Dr. Brooks is employed by Queen's University, provided expert testimony for Stieber Berlach LLP (expert witness for the defense in a civil case involving the nonuse of an automated external defibrillator during an out-of-hospital cardiac arrest), received grant support from the Heart and Stroke Foundation of Canada (HSFC; peer-reviewed operating grants for studies involving knowledge translation interventions in cardiac arrest), and received support for travel from the American Heart Association (AHA; Reimbursement for expenses related to Science Subcommittee membership–volunteer position). Dr. Goodman consulted for AstraZeneca, Bayer, Eli Lilly, and Sanofi Aventis; lectured for AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, and Sanofi; received support for the development of educational presentations from AstraZeneca and Bayer; and received salary support from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair in Cardiology. Dr. Goodman and his institution received grant support from AstraZeneca, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, and Sanofi (research and unrestricted educational grant support) and received research grant support from the Canadian Heart Research Centre, Canadian VIGOUR Centre, and Duke Clinical Research Institute. Dr. Morrison has received operating grants from CIHR, HSFC, AHA, Ministry of Health and Long-Term Care of Ontario, Laerdal, and Defence Research and Development Canada. She was also a past chair and current member of the AHA Emergency Cardiovascular Care committee, a member of the Editorial Board of the 2010 AHA resuscitation guidelines, and was the co-chair of the C2010 and is the current co-chair of the C2015 ILCOR advanced life support taskforce. She received support for article research from the National Institutes of Health. Her institution received grant support from the PSIF (resident research grant). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000000551

Objectives: Targeted temperature management has been shown to improve survival with good neurological outcome in patients after out-of-hospital cardiac arrest. The optimal approach to inducing and maintaining targeted temperature management, however, remains uncertain. The objective of this study was to evaluate these processes of care with survival and neurological function in patients after out-of-hospital cardiac arrest.

Design: An observational cohort study evaluating the association of targeted temperature management processes with survival and neurological function using bivariate and generalized estimating equation analyses.

Setting: Thirty-two tertiary and community hospitals in eight urban and rural regions of southern Ontario, Canada.

Patients: Consecutive adult (≥ 18 yr) patients admitted between November 1, 2007, and January 31, 2012, and who were treated with targeted temperature management following nontraumatic out-of-hospital cardiac arrest.

Interventions: Evaluate the association of targeted temperature management processes with survival and neurologic function using bivariate and generalized estimating equation analyses.

Measurements and Main Results: There were 5,770 consecutive out-of-hospital cardiac arrest patients, of whom 747 (12.9%) were eligible and received targeted temperature management. Among patients with available outcome data, 365 of 738 (49.5%) survived to hospital discharge and 241 of 675 (35.7%) had good neurological outcomes. After adjusting for the Utstein variables, a higher temperature prior to initiation of targeted temperature management was associated with improved neurological outcomes (odds ratio, 1.27 per °C; 95% CI, 1.08–1.50; $p = 0.004$) and survival (odds ratio, 1.26 per °C; 95% CI, 1.09–1.46; $p = 0.002$). A slower rate of cooling was associated with improved neurological outcomes (odds ratio, 0.74 per °C/hr; 95% CI, 0.57–0.97; $p = 0.03$) and survival (odds ratio, 0.73 per °C/hr; 95% CI, 0.54–1.00; $p = 0.049$).

Conclusions: A higher baseline temperature prior to initiation of targeted temperature management and a slower rate of cooling were associated with improved survival and neurological outcomes. This may reflect a complex relationship between the approach to targeted temperature management and the extent of underlying brain injury causing impaired thermoregulation in out-of-hospital cardiac arrest patients. (*Crit Care Med* 2014; XX:00–00)

Key Words: advanced cardiac life support; body temperature; heart arrest; hypothermia; out-of-hospital cardiac arrest; resuscitation

Out-of-hospital cardiac arrest (OHCA) remains a significant cause of death worldwide. The average survival rate in OHCA treated by emergency medical services (EMS) ranges from approximately 8% to 11% (1–4), although variation exists and is thought to reflect variability in OHCA risk factors, prehospital interventions (including local approaches to organizing EMS responses), and differences in post–cardiac arrest care (3).

Targeted temperature management (TTM), also referred to as "therapeutic hypothermia," is one of the few in-hospital treatments that has been demonstrated in randomized clinical trials to improve rates of survival with good neurological outcome in OHCA patients (5–7). Despite the available evidence suggesting that post–cardiac arrest patients should receive TTM (8, 9), the optimal approach to inducing, maintaining, and discontinuing this treatment remains unclear. Specifically, data on where to start TTM, how fast to cool, how cold to cool, how long to cool, and how to rewarm are currently derived mainly from animal studies (10–14) and few clinical studies (5–7, 15–20) with inconsistent findings.

The objective of this study was to describe and evaluate the associations between the processes of performing TTM, specifically related to the induction and maintenance phases of TTM (21), and patient survival and neurological outcomes following OHCA.

MATERIALS AND METHODS

Study Design, Setting, and Population

We conducted an observational cohort study merging two databases: the Toronto regional site of the Resuscitation Outcomes Consortium (ROC) Epistry–Cardiac Arrest (22, 23) and the Strategies for Post Arrest Resuscitation Care (SPARC) Network databases (24). The Toronto regional ROC-Epistry cardiac arrest database is a prospective population-based registry of consecutive, OHCA patients treated by paramedic providers of EMS agencies serving eight urban and rural regions of Ontario, Canada: Durham, Hamilton, Halton, Muskoka, Peel, Simcoe, Toronto, and York and encompassing a population of approximately 8.8 million people (23, 25). The SPARC Network trial (NCT00683683) implemented a knowledge translation (KT) program to improve the delivery of care to post–cardiac arrest patients treated at 32 southern Ontario hospitals, all of which are currently destination hospitals for the EMS agencies participating in the Toronto regional ROC cardiac arrest registry (24, 26).

All adult (≥ 18 yr) patients who suffered an OHCA of presumed cardiac etiology (all initial rhythms) prior to EMS arrival between November 1, 2007, and January 31, 2012, were eligible for study inclusion. Patients included in the study were treated and transported by advanced or basic paramedic providers to a destination hospital, had a sustained return of spontaneous circulation (ROSC) of greater than or equal to 20 minutes, and received TTM in-hospital.

The SPARC Network trial was approved by the research ethics boards of all participating 32 hospitals.

Study Variables and Outcomes

Patient and Cardiac Arrest Variables. We considered all available patient and cardiac arrest variables that conformed to the Utstein recommendations for standardized OHCA and postresuscitation reporting (27–29).

Temperature Measurements. We collected hourly temperature measurements; where gaps existed in temperature measurements during TTM, we used linear interpolation to estimate the time points during which a patient's temperature was in the target range (≤ 34°C). All temperatures were measured by a core (e.g., esophageal, bladder, rectal, intravascular, or unspecified core method), a peripheral (e.g., tympanic, oral, skin, or axillary), or an unspecified method. Patients who had a spontaneous baseline temperature that was already less than or equal to 34°C following sustained ROSC were excluded in analyses of factors related to TTM induction.

TTM Variables. The temperature-related variables of interest were divided into the TTM induction phase and TTM maintenance phase (**Table 1**).

Outcomes. The primary outcome was survival with good neurological outcome at hospital discharge, defined as a score of 0 to 3 on the 7-point Modified Rankin Scale (MRS) (30, 31). The secondary outcome was survival to hospital discharge.

Sensitivity and Subgroup Analyses. We conducted a sensitivity analysis using only temperatures measured by a core method

TABLE 1. Temperature Process Variables Related to Targeted Temperature Management Induction and Maintenance

Variable	Definition
TTM induction variables	
Location of TTM initiation	TTM initiation either in the emergency department or ICU
Temperature prior to TTM (°C)	Last spontaneous temperature recorded prior to TTM initiation
Time to target temperature of 34°C (hr)	Time duration between TTM initiation and patient reaching target temperature of 34°C
Rate of cooling (°C/hr)	Temperature difference between the temperature prior to TTM and 34°C, divided by the time to target temperature of 34°C[a]
TTM maintenance variables	
Total TTM duration (hr)	Time duration of patient temperature ≤ 34°C during TTM maintenance phase[b]
TTM time product (°C × hr)	Total area under the curve ≤ 34°C during TTM maintenance phase[c]

TTM = targeted temperature management.

[a]Patients with spontaneous baseline temperatures ≤ 34°C following sustained return of spontaneous circulation were excluded.

[b]Time duration of temperature fluctuations > 34°C were excluded.

[c]Area under the curve: *x*-axis, time (hr); *y*-axis, temperature (°C). Temperature fluctuations > 34°C were excluded (**Fig. S1**, Supplemental Digital Content 1, which describes an example calculation of the TTM time product).

(e.g., esophageal, bladder, rectal, intravascular, or unspecified core method). We also considered a more conservative definition of good neurological outcome defined as an MRS of 0 to 2 compared to poor neurological outcome defined as an MRS of 3 to 5 and excluding deaths during hospital admission. To create a cohort more comparable to the clinical trials supporting the use of TTM (5, 6), we considered a subgroup comprised only of patients who had a bystander-witnessed OHCA with ventricular fibrillation or pulseless ventricular tachycardia as the initial cardiac rhythm and excluded those with a temperature less than 30°C prior to the initiation of TTM.

Statistical Analyses

Published data on rates of cooling at the time of study conception were lacking to inform our power calculations (15–17). However, our sample size of 740 has 80% power at a of 0.05 to detect an odds ratio (OR) of 0.76 for survival. This OR corresponds to a change in the probability of survival from the baseline value of 0.2 at the mean time to target temperature to 0.16 when time to target temperature is increased to 1 SD above the mean. This calculation also incorporated an adjustment for an r^2 of 0.1 for the correlation between independent variables of interest and the other independent variables in the logistic regression (32). The calculation was performed using PASS Version 8.0.8 (Hintze J, 2008, PASS 2008, NCSS, Kaysville, UT).

We performed univariate analyses on the TTM process and Utstein variables. The distribution of each continuous variable (e.g., age) was first assessed for normality using both graphical interpretation and the Shapiro-Wilk test. Means with SDs or medians with interquartile ranges were reported for normally and nonnormally distributed variables, respectively. Categorical variables were reported using counts and proportions. Bivariate analyses were performed to compare the predictor variables and outcomes. Depending on the distribution of each predictor variable, a t test or Wilcoxon rank-sum test was used to compare continuous data. Chi-square or Fisher exact tests were performed, as appropriate, to assess the difference between categorical variables.

Our primary analyses involved a series of generalized estimating equations (GEE) to assess the relationship between the predictor variables and the primary and secondary outcomes after adjusting for the core Utstein variables and to account for any potential effects of clustering of patients within hospitals. The final GEE models included both TTM induction and maintenance phase variables. When patients were transferred between hospitals, the patient's first hospital was used as their cluster for analysis purposes. An intracluster correlation coefficient (ICC) was calculated for each binary outcome as a measure of the relatedness of clustered data by comparing the variance between clusters (33, 34). We calculated the Quasi-likelihood under the independence model criterion as a measure of the fit of the independent variables in modeling the respective outcome in GEE (35). The "significance-test-of-the-difference" strategy was used to test each predictor variable for inclusion, and predictor variables were included in the GEE model, if their respective β-coefficient were significant using a conservative p value of 0.25 (36). Multicollinearity was assessed by the variance inflation factor (VIF) of all predictor variables and covariates to avoid including highly correlated independent variables into the GEE. The investigator group reviewed each set of highly correlated predictor variables and covariates with values of VIF greater than 2.5 and selected one of the variables to include in the model based on its clinical significance. We tested an a priori statistical interaction between temperature prior to TTM and age, and in a post hoc analysis, we tested the interaction of temperature prior to TTM with time to target temperature and with rate of cooling. If the interaction terms were statistically significant, the term was included in the GEE analysis. Receiver operating characteristic curves with corresponding *c*-statistics were generated using predicted values from the final GEE models to assess discrimination. Temperature calculations and statistical analyses were performed using Microsoft Excel 2010 (Redmond, WA) and SAS version 9.2 (SAS Institute, Cary, NC), respectively.

RESULTS

Patient Characteristics

There were a total of 5,770 consecutive OHCA patients transported to the 32 hospitals in the SPARC network during the study period, and 1,274 (22.1%) were eligible for TTM. Of these, 747 patients (58.6%) received TTM and were included in the study (**Fig. 1**). Data required to estimate rates of survival to hospital discharge and MRS at hospital discharge were available for 738 (98.8%) and 675 (90.4%) patients, respectively. Baseline distribution of Utstein covariates and unadjusted outcome data are shown in **Tables 2 and 3**, and adjusted outcome data are shown in **Tables S1 and S2** (Supplemental Digital Content 1, http://links.lww.com/CCM/B39), which describes the unadjusted and adjusted odds ratios of the Utstein variables for good neurological outcome and survival to hospital discharge, respectively. Linear interpolation was used to estimate 2,914 of 43,072 (6.8%) of temperature time points at 34°C. The ICC values for survival with good neurological outcome and survival to hospital discharge were 0.024 and 0.018, respectively, suggesting that differences in these outcomes were not largely influenced by hospital level effects.

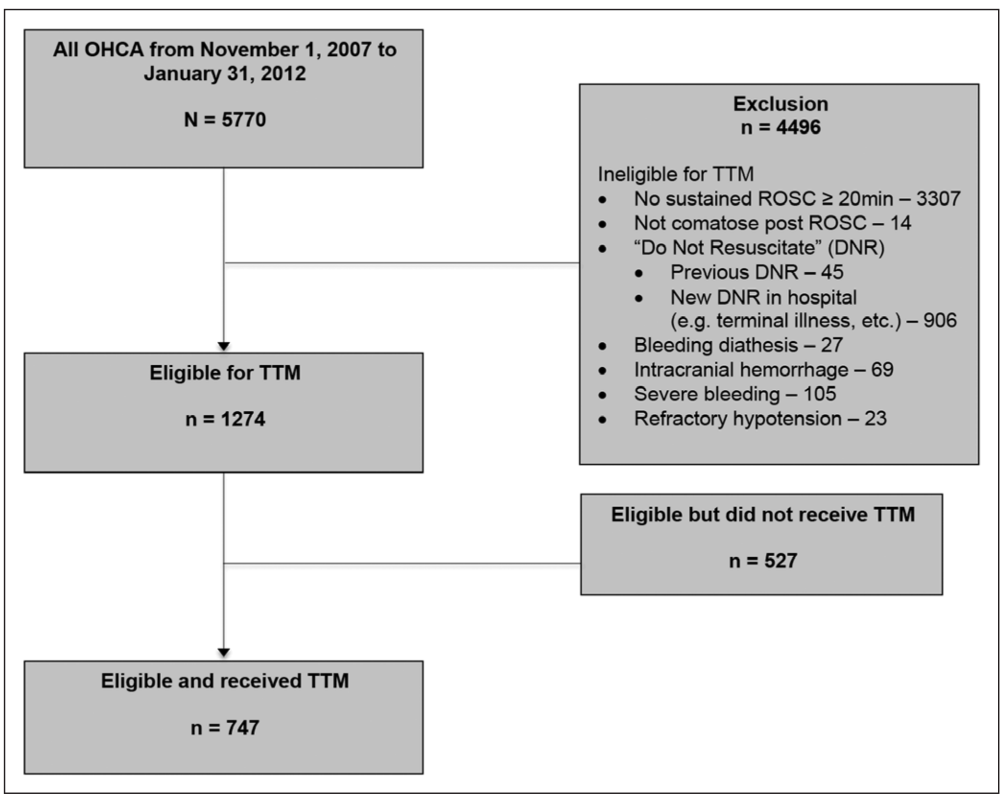

Figure 1. Flow diagram of the included study population. DNR = do not resuscitate, OHCA = out-of-hospital cardiac arrest, ROSC = return of spontaneous circulation, TTM = targeted temperature management.

TTM Induction Phase

Location of TTM Initiation. The proportion of patients who survived with good neurological outcome or survived to hospital discharge did not differ depending on whether TTM was initiated in the ICU or in the emergency department (**Table 4**). The location of TTM initiation was not associated with good neurological outcome (OR, 1.04; 95% CI, 0.76–1.43; $p = 0.81$) or survival to discharge (OR, 1.17; 95% CI, 0.87–1.56; $p = 0.30$).

Temperature Prior to TTM. Patients who survived with good neurological outcome and those who survived to hospital discharge had significantly higher temperatures prior to TTM compared with patients with poor neurological outcome or those who died (Table 4). Similarly, a higher temperature prior to TTM was associated with higher odds of surviving with good neurological outcome and surviving to hospital discharge in both the unadjusted and adjusted analyses (**Table 5**), and also in the final GEE model, which included variables from both the induction and maintenance phases of TTM (**Table 6**). There was no statistical interaction between temperature prior to TTM and age, time to target temperature, or rate of cooling.

Time to Target Temperature. There was no significant difference in time to target temperature comparing patients who survived with good neurological outcome and those who did not (Table 4). Time to target temperature was not associated with survival with good neurological outcome (Table 5). The time to target temperature in patients who survived to hospital discharge was longer (Table 4), but its association with increased survival was no longer significant after adjusting for the Utstein variables (Table 5).

Rate of Cooling. The rate of cooling was not statistically different comparing patients surviving with good neurological outcome to those who did not or comparing those who survived to those who died (Tables 4 and 5). However, in the final GEE model, a slower rate of cooling was significantly associated with good neurological outcome and survival to discharge (Table 6).

Maintenance Phase Variables

Total TTM Duration. The total TTM duration was significantly shorter in patients who survived with good neurological outcome compared with those who did not and in patients who survived to hospital discharge compared with patients who died (Table 4). However, duration of TTM was only associated with

TABLE 2. Characteristics of Included Study Patients

Variable	All Out-of-Hospital Cardiac Arrest Patients (%) n = 5,770[a]	All Eligible Patients for TTM (%) n = 1,274[b]	Eligible Patients Who Received TTM (%) n = 747[c]
Age			
Median (IQR), yr	69 (57, 80)	66 (54, 77)	63, (53, 75)
Gender			
Male	3,953 (68.5%)	902 (70.8%)	546 (73.1%)
Initial cardiac rhythm[d]			
Ventricular fibrillation/ pulseless ventricular tachycardia	2,102 (36.4%)	757 (59.4%)	504 (67.5%)
Location			
Public	1,441 (25.0%)	453 (35.6%)	264 (35.3%)
Witness status			
Bystander-witnessed	3,217 (55.8%)	894 (70.2%)	524 (70.1%)
Bystander cardiopulmonary resuscitation			
Yes	2,355 (40.8%)	629 (49.4%)	370 (49.5%)
Emergency medical services response time			
Median (IQR), min	6.0 (4.9, 7.2)	5.7 (4.7, 6.9)	5.6 (4.7, 6.8)

TTM = targeted temperature management, IQR = interquartile range.

[a]Missing data in all out-of-hospital cardiac arrest population: gender in 6 (0.1%), location in 14 (0.2%), witness status in 62 (1.1%), cardiopulmonary resuscitation (CPR) in 107 (1.9%), emergency medical services (EMS) response times in 475 (8.2%), initial cardiac rhythm in 105 (1.8%), and survival in 24 (0.4%) patients.

[b]Missing data in all eligible for cooling population: location in 4 (0.3%), witness status in 12 (0.9%), CPR in 26 (2.0%), EMS response times in 104 (8.2%), initial cardiac rhythm in 39 (3.1%), and survival in 16 (1.3%) patients.

[c]Missing data in all eligible and cooled population: location in 2 (0.3%), witness status in 8 (1.1%), CPR in 13 (1.7%), EMS response times in 57 (7.6%), initial cardiac rhythm in 8 (1.1%), and survival in 9 (1.2%) patients.

[d]Cardiac rhythm determined by an EMS defibrillator or automated external defibrillator (AED) or by a non-EMS AED.

survival in the unadjusted analysis, and this association was no longer statistically significant after adjusting for the Utstein covariates (Tables 5 and 6).

TTM Time Product. The TTM time product was significantly smaller in patients who survived with good neurological outcome compared with those who did not and in patients who survived to hospital discharge compared with patients who died (Table 4). A smaller TTM time product was associated with both survival with good neurological outcome and survival to discharge in the unadjusted analyses but not after adjusting for the Utstein variables (Table 5). When the total TTM duration was replaced with the TTM time product as the TTM maintenance variable in the final GEE, the TTM time product was not significantly associated with neurological outcome or survival to discharge (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B39, which describes the adjusted odds ratios of TTM induction and maintenance variables using the TTM time product instead of the total TTM duration).

Sensitivity and Subgroup Analyses

In a sensitivity analysis of 693 of 747 patients (92.8%) with available core temperature measurements during TTM, there were no differences in the associations found between time to target temperature, rate of cooling, or TTM duration less than or equal to 34°C, and survival with good neurologic outcome (MRS 0–3) and survival to hospital discharge, respectively, compared to the primary analyses (**Tables S4 and S5**, Supplemental Digital Content 1, http://links.lww.com/CCM/B39, which describes the bivariate analyses, and unadjusted and adjusted odds ratios of the TTM induction and maintenance variables using only core-measured temperatures). When we redefined good neurological outcome as MRS 0–2 and excluded deaths, the results did not differ substantially from our main findings (**Tables S6–S8**, Supplemental Digital Content 1, http://links.lww.com/CCM/B39, which describes the bivariate analyses and unadjusted odds ratios of the Utstein, and TTM induction and maintenance variables when good neurological outcome was defined as MRS 0–2). In the subgroup analysis using a study population similar to the Hypothermia After Cardiac Arrest trial (5) and after adjusting for the Utstein variables, a higher temperature prior to TTM was significantly associated with survival with good neurological outcome (OR, 1.22; 95% CI, 1.01–1.48; p = 0.04). Survival to hospital discharge in this subgroup was associated with

TABLE 3. Bivariate Analyses of Utstein Variables in Patients Who Received Targeted Temperature Management[a]

Variable	MRS 0–3 *n* = 241	MRS 4–6 *n* = 434	p^b	Survived to Discharge *n* = 365	Dead *n* = 373	p^b
Age						
Median (IQR), yr	58 (49, 66)	68 (55, 78)	< 0.0001	59 (50, 69)	70 (57, 79)	< 0.0001
Gender						
Male	184 (76.3%)	306 (70.5%)	0.10	283 (77.5%)	257 (68.9%)	0.008
Initial cardiac rhythm[c]						
Ventricular fibrillation/pulseless ventricular tachycardia	220 (91.3%)	224 (51.6%)	< 0.0001	315 (86.3%)	182 (48.8%)	< 0.0001
Location						
Public	104 (43.2%)	125 (28.8%)	0.0001	163 (44.7%)	97 (26.0%)	< 0.0001
Witness status						
Bystander-witnessed	200 (83.0%)	277 (63.8%)	< 0.0001	287 (78.6%)	230 (61.7%)	< 0.0001
Bystander cardiopulmonary resuscitation						
Yes	135 (56.0%)	199 (45.9%)	0.02	202 (55.3%)	162 (43.4%)	0.003
Emergency medical services response time						
Median (IQR), min	5.4 (4.6, 6.3)	5.8 (4.7, 7.0)	0.01	5.4 (4.5, 6.3)	5.8 (4.8–7.1)	0.0002

MRS = Modified Rankin Scale, IQR = interquartile range.

[a]MRS data were missing in 72 patients and survival data were missing in nine patients.

[b]Differences between groups were analyzed using the Wilcoxon rank-sum test for continuous data and the chi-square test for categorical data.

[c]Cardiac rhythm determined by an emergency medical services (EMS) defibrillator or automated external defibrillator (AED) or by a non-EMS AED.

higher patient temperatures prior to TTM, shorter duration of TTM, and smaller TTM time product in the unadjusted analysis (**Tables S9 and S10**, Supplemental Digital Content 1, http://links.lww.com/CCM/B39, which describes the bivariate analyses of the Utstein variables, and the unadjusted and adjusted odds ratios of the TTM induction and maintenance variables in a study subpopulation similar to the HACA trial).

DISCUSSION

In this study of adult OHCA patients who received TTM, we evaluated the processes of care related to performing TTM such as the location of TTM initiation, temperature prior to TTM initiation, time to target temperature, rate of cooling, TTM duration, and the TTM time product. We found that a higher temperature prior to TTM initiation and a slower rate of cooling were both independently associated with good neurological outcome and survival to hospital discharge.

Patients with higher baseline temperatures prior to TTM were significantly associated with good neurological outcome and survival, a finding that is similar to previous studies (17, 20, 37, 38). Baseline temperatures may represent the extent of neurological insult after anoxic and reperfusion injury of OHCA, a relationship that has also been recognized in patients with traumatic brain injuries (39, 40). Although the mechanism remains unclear, it is hypothesized that hypothalamic dysfunction and impairment of thermoregulatory pathways in OHCA may lead to lower body temperature. Global ischemia and reperfusion injury may damage vasomotor pathways in the skin, leading to perturbed vasoconstriction/vasodilation and inappropriate heat loss, particularly after prolonged durations of cardiac arrest. Future OHCA studies should report patient baseline temperatures post ROSC as a standard variable.

A slower rate of cooling was also associated with good neurological outcome and survival. Compared to measuring time to target temperature, the rate of cooling is not affected by the baseline temperature post ROSC and therefore may better reflect the rapidity of patient temperature change. However, the meaning of faster rates of cooling remains unclear. A recent prehospital randomized controlled trial showed a nonsignificant trend toward survival benefit using a fast transnasal

TABLE 4. Bivariate Analyses of Targeted Temperature Management Induction and Maintenance Temperature Variables

Variable	MRS 0–3	MRS 4–6	p[a]	Survival to Discharge	Dead	p[a]
Location of TTM initiation						
ICU, %	42.7	41.8	0.81	44.9	41.1	0.30
Temperature prior to TTM						
Median (IQR), °C	36.0 (35.4, 36.7)	35.7 (34.7, 36.4)	0.0002	36.1 (35.4, 36.7)	35.6 (34.6, 36.4)	< 0.0001
Time to target temperature of 34°C						
Median (IQR), hr	4.0 (2.3, 6.3)	3.5 (1.6, 6.3)	0.11	4.3 (2.4, 6.8)	3.4 (1.5, 5.8)	0.001
Rate of cooling						
Median (IQR), °C/hr	0.52 (0.27, 0.86)	0.48 (0.26, 0.91)	0.69	0.49 (0.27, 0.81)	0.50 (0.27, 0.95)	0.54
Total TTM duration						
Median (IQR), hr	15.8 (8.3, 21.6)	18.1 (6.6, 24.5)	0.04	15.7 (7.6, 22.2)	18.7 (7.0, 24.7)	0.006
TTM time product						
Median (IQR), °C × hr	16.7 (6.3, 23.8)	19.3 (4.1, 31.1)	0.03	16.2 (4.9, 23.9)	20.5 (4.5, 31.3)	0.001

MRS = Modified Rankin Scale, TTM = targeted temperature management, IQR = interquartile range.
[a]Differences between groups were analyzed using the Wilcoxon rank-sum test between the MRS 0–3 and 4–6 and survival to discharge and dead groups, respectively.

evaporative cooling device (41), and a similar benefit was seen in an observational study of a fast convective-immersion surface cooling device (42). A faster rate of cooling may also represent the extent of impaired thermoregulation after cardiac arrest. The loss of physiological counterregulatory mechanisms to induced hypothermia may represent the severity of insult and may be reflected, in part, as a faster rate of cooling. Future clinical trials are needed to help elucidate this complex

TABLE 5. Unadjusted and Adjusted for Utstein Variables Odds Ratios of Targeted Temperature Management Induction and Maintenance Temperature Variables for Good Neurological Outcome (Modified Rankin Scale 0–3) and Survival to Hospital Discharge

	Unadjusted OR (95% CI)				Adjusted OR (95% CI)[a]			
Variable	MRS 0–3	p	Survival to Discharge	p	MRS 0–3	p	Survival to Discharge	p
Temperature prior to TTM (°C)	1.28 (1.11–1.48)	0.001	1.29 (1.13–1.47)	0.0002	1.21 (1.07–1.36)	0.002	1.22 (1.06–1.40)	0.004
Time to target temperature of 34°C (hr)	1.03 (0.98–1.07)	0.23	1.06 (1.01–1.11)	0.01	1.02 (0.97–1.08)	0.44	1.05 (0.99–1.10)	0.10
Rate of cooling (°C/hr)	0.89 (0.67–1.19)	0.49	0.78 (0.59–1.04)	0.09	0.85 (0.63–1.13)	0.27	0.78 (0.58–1.04)	0.09
Total TTM duration (hr)	0.97 (0.97–1.00)	0.07	0.98 (0.97–0.99)	0.01	1.00 (0.98–1.02)	0.78	0.99 (0.97–1.01)	0.39
TTM time product (°C × hr)	0.98 (0.97–1.00)	0.005	0.98 (0.97–0.99)	< 0.0001	1.00 (0.98–1.01)	0.63	0.99 (0.98–1.00)	0.17

OR = odds ratio, MRS = Modified Rankin Scale, TTM = targeted temperature management.
[a]Generalized estimating equation models converged.

TABLE 6. Final Generalized Estimating Equations of Combined Targeted Temperature Management Induction and Maintenance Temperature Variables for Good Neurological Outcome (Modified Rankin Scale 0–3) and Survival to Hospital Discharge

	Modified Rankin Scale 0–3[a]		Survival[b]	
Variable	OR (95% CI)	p	OR (95% CI)	p
Age (yr)	0.96 (0.94–0.98)	< 0.0001	0.96 (0.94–0.97)	< 0.0001
Male vs female	0.99 (0.56–1.75)	0.96	1.15 (0.72–1.84)	0.55
Ventricular fibrillation/pulseless ventricular tachycardia vs pulseless electrical activity/asystole[c]	8.03 (2.94–21.92)	< 0.0001	4.20 (2.00–8.82)	0.0002
Public vs nonpublic location	1.21 (0.85–1.74)	0.29	1.49 (0.93–2.39)	0.10
Bystander-witnessed vs unwitnessed	1.73 (0.96–3.13)	0.07	1.43 (0.74–2.76)	0.28
Bystander CPR vs no bystander CPR	1.20 (0.57–2.51)	0.63	1.15 (0.68–1.93)	0.61
Emergency medical services response time (min)	0.93 (0.78–1.10)	0.39	0.82 (0.69–0.96)	0.02
Temperature prior to TTM (°C)	1.27 (1.08–1.50)	0.004	1.26 (1.09–1.46)	0.002
Rate of cooling (°C/hr)	0.74 (0.57–0.97)	0.03	0.73 (0.54–1.00)	0.049
Total TTM duration (hr)	0.98 (0.96–1.01)	0.26	0.99 (0.96–1.02)	0.39

OR = odds ratio, CPR = cardiopulmonary resuscitation, TTM = targeted temperature management.

[a]Generalized estimating equation model converged, $n = 284$, quasi-likelihood under the independence model criterion (QIC) = 323, c-statistic = 0.80.

[b]Generalized estimating equation model converged, $n = 310$, QIC = 357, c-statistic = 0.79.

[c]Cardiac rhythm determined by an emergency medical services (EMS) defibrillator or automated external defibrillator (AED) or by a non-EMS AED.

relationship and determine the optimal rate of cooling in OHCA patients.

Similar to previous studies, we did not observe an association between the depth and duration of TTM during the maintenance phase and patient outcomes (7, 18, 19, 43). We recognized, however, that the effects of TTM are likely related to a complex relationship between the depth and duration of TTM. In this study, we proposed a novel measure called the "TTM time product," a measure similar to the fever burden in neurological trauma (44) and stroke patients (45, 46). The TTM time product, calculated as the area under the curve less than or equal to 34°C, accounts for temperature fluctuations greater than 34°C and reflects both the duration and depth of TTM (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B39, which describes an example calculation of the TTM time product). Although the TTM time product was not associated with patient outcomes in the adjusted analyses, we may have lacked statistical power to evaluate small but clinically important differences. We believe this novel measure may best represent the relationship between the depth and duration of TTM and may serve as a new measure in future studies in post–cardiac arrest care.

To our knowledge, this was the largest North American study evaluating the processes of care related to performing TTM in OHCA patients. It was based on multicenter, research-quality clinical datasets, which form one of the largest postresuscitation registries in the world. The SPARC KT trial (results not yet published) aimed to improve the use of TTM at 32 hospitals, and in the study, 58.6% of eligible patients received TTM. Although there continues to be barriers in adopting TTM in post–cardiac arrest patients (47), this also represents a significant improvement compared to previous studies (48, 49). This was also the first study in post–cardiac arrest research to propose the use of linear interpolation to estimate time intervals at or below the target temperature, which helped define the time to target temperature, rate of cooling, duration less than or equal to 34°C, and the TTM time product. In addition, we also accounted for any fluctuations greater than 34°C during TTM in our analyses and employed complex statistical methods for risk adjustment that consider the variance between hospitals clusters when evaluating associations between processes and outcomes.

Similar to all observational studies, there were a number of limitations of the current study. Unmeasured or unaccounted confounders present a challenge to all observational studies. The selected confounders used in this study were based on the standardized core Utstein variables for standard reporting (27, 29). There were also missing data on several variables (Tables 2 and 3), including MRS. Although we believe that most missing data were due to randomly missing documentation in the source charts, it is possible that reasons for missing some data were associated with specific patient characteristics or outcomes, which could bias our findings. Our study included temperature measurements from peripheral methods, which may differ up to 3°C (50). To address and reduce the risk of insensitive measure bias, we performed a sensitivity analysis on the predictor variables of interest using only core temperature measurements and found no significant differences in the findings of our primary analysis. Our databases are population-based registries of eight urban and rural regions in Canada, but our results may not be generalizable to other EMS and hospital systems where other process factors may be more important. The low ICC values, however, suggest that differences in patient outcomes were mainly due to patient and process level characteristics and not due to hospital level characteristics. Lastly, our study cannot be used to evaluate the relative efficacy of TTM, since we only included patients who received this therapy.

CONCLUSIONS

A higher baseline temperature prior to TTM and a slower rate of cooling were associated with improved survival with good neurological outcomes and survival to hospital discharge. This may reflect the complex relationship between the TTM techniques used and the extent of hypothalamic dysfunction and impaired thermoregulation in patients after cardiac arrest. Future trials should measure and report baseline temperature measurements post ROSC. More research is needed to assess the optimal rate of cooling, temperature target, and TTM duration to achieve the best neurological survival after OHCA.

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