Comparative Effectiveness of Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest: Insight from a Large Data Registry

Timothy J. Mader,¹ Brian H. Nathanson,² William E. Soares III,¹ Ryan A. Coute,¹
Bryan F. McNally;³ for the CARES Surveillance Group

This study was done to determine the effectiveness of therapeutic hypothermia (TH) after out-of-hospital cardiac arrest (OHCA) among a large cohort of adults in the Cardiac Arrest Registry to Enhance Survival (CARES), with an emphasis on subgroups with a nonshockable first documented rhythm. This was an IRB approved retrospective cohort study. All adult index events at participating sites from November 2010 to December 2013 were study eligible. All patient data elements were provided. Summary statistics were calculated for all patients with and without TH. For multivariate adjustment, a multilevel (i.e., hierarchical), mixed-effects logistic regression (MLR) model was used with hospitals treated as random effects. Propensity score matching (PSM) on both shockable and nonshockable patients was done as a sensitivity analysis. After predefined exclusions, our final sample size was 6369 records for analysis: shockable=2992 (47.0%); asystole=1657 (26.0%); pulseless electrical activity=1249 (19.6%); other unspecified nonshockable=471 (7.4%). Unadjusted differences in neurological status at hospital discharge with and without TH were similar ($p=0.295$). After multivariate adjustment, TH had either no association with good neurological status at hospital discharge or that TH was actually associated with worse neurological outcome, particularly in patients with a nonshockable first documented rhythm (i.e., for NS patients, MLR odds ratio for TH=1.444; 95% CI [1.039, 2.006] $p=0.029$, and OR=1.017, $p=0.927$ via PSM). Highlighting our limitations, we conclude that when TH is indiscriminately provided to a large population of OHCA survivors with a nonshockable first documented rhythm, evidence for its effectiveness is diminished. We suggest more uniform and rigid guidelines for application.

Introduction

AMONG OUT-OF-HOSPITAL CARDIAC ARREST (OHCA) survivors, prolonged cerebral ischemia with subsequent reperfusion injury is a significant cause of postresuscitation mortality and long-term neurological disability (Edgren *et al.*, 1994). Since 2005, targeted temperature management or therapeutic hypothermia (TH), defined as whole body cooling to 32–34°C for 12–24 hours, has been recommended for comatose adults recovering from ventricular fibrillation (VF) OHCA in an attempt to attenuate reperfusion injury, preserve neurological function, and improve quality survival (ECC Committee and Subcommittees and Task Forces of the American Heart Association, 2005). Over the last decade, TH has emerged as a standard treatment in the care of comatose adults recovering from VF OHCA and is now often extrapolated beyond its proven indications to patients who were

specifically excluded from the randomized controlled trials—most notably, patients with a nonshockable first documented rhythm (asystole or pulseless electrical activity [PEA]) (Kim *et al.*, 2012).

The consequence of TH after OHCA due to a nonshockable rhythm is still uncertain (Walters *et al.*, 2011), and as of 2010, it retains a Class IIb (LOE B) recommendation (Peberdy *et al.*, 2010). Recently, a large systematic review and meta-analysis of clinical studies, including 10 with neurological outcomes reported, suggested minimal if any benefit of TH for patients with a nonshockable first documented rhythm (Kim *et al.*, 2012). Since then, six additional case series with somewhat conflicting, but similar results have been published (Dumas *et al.*, 2011; Testori *et al.*, 2011; Kory *et al.*, 2012; Lundbye *et al.*, 2012; Soga *et al.*, 2012; Storm *et al.*, 2012).

This was a retrospective cohort study, done to compare resuscitation outcomes after OHCA resuscitation among a

¹Department of Emergency Medicine, Baystate Medical Center, Tufts University School of Medicine, Springfield, Massachusetts.

²OptiStatim, LLC, Longmeadow, Massachusetts.

³Department of Emergency Medicine, Emory University School of Medicine, Atlanta, Georgia.

large cohort of adults in the Cardiac Arrest Registry to Enhance Survival (CARES) (<https://mycares.net>) dataset to determine the effectiveness of TH compared with standard treatment (No-TH) in OHCA survivors, with an emphasis on subgroups of those with a nonshockable first documented rhythm. Our central hypothesis, based on our literature review and preliminary data analysis, was that TH provision after OHCA compared with No-TH would be associated with a modest, but favorable neurological status at hospital discharge and that the effect would vary by rhythm classification (shockable vs. asystole vs. PEA).

Materials and Methods

The study was reviewed and approved by the Institutional Review Board (183049-6) through expedited review.

Design, setting, and population

Initiated in 2004, CARES is a collaborative effort of the Centers for Disease Control and Prevention and the Emory University Department of Emergency Medicine with private funding occurring in 2012 (McNally *et al.*, 2009). Using the Utstein style of reporting on OHCA (Cummins *et al.*, 1991; Jacobs *et al.*, 2004), CARES was developed to serve as a central repository of data and a quality improvement tool on OHCA for Emergency Medical Service (EMS) systems throughout the United States. The registry focuses on a relatively small number of key prehospital variables that can be objectively measured, are clearly defined, and are known to affect patient outcomes (McNally *et al.*, 2009). The program is capable of identifying and tracking all consecutive cases of cardiac arrest in a defined geographic area through the continuum of care from EMS activation to hospital discharge. There are currently more than 400 EMS agencies and 900 hospitals participating across the United States with a catchment of over 50 million people (Appendix 1). The CARES design, development, and data elements included have been published previously and described in great detail (McNally *et al.*, 2009).

This was a secondary analysis of prospectively collected data submitted to CARES from November 1, 2010, which is when TH became a mandatory reporting field, to December 31, 2012. All adult (≥ 18 years of age) index arrests of presumed cardiac etiology with attempted resuscitation at participating sites were screened for study eligibility. Sustained return of spontaneous circulation (ROSC) with survival to hospital admission was a prerequisite for study inclusion. The cohort was defined by cooling in the field that was continued after hospital admission or cooling initiated after hospital arrival and continued during hospitalization. All records with missing TH status or outcome classification were excluded. Furthermore, we excluded patients whose arrest occurred in a long-term care facility as a surrogate for likely poor baseline health status potentially negatively biasing the hypothermia group toward poor outcomes. Finally, we excluded patients whose arrest occurred after arrival of EMS as a surrogate for likely short arrest duration to reduce bias toward good outcomes in the control (No-TH) group. All remaining records were categorized as shockable (i.e., VF, pulseless ventricular tachycardia or other unspecified shockable rhythm), asystole, PEA, or other unspecified nonshockable rhythm for analysis based on the patients' first documented rhythm. All data el-

ements in the registry relevant to the research question were considered for modeling.

Data collection and processing

Prehospital providers initiate a CARES event based on criteria set forth by the project coordinator and the data dictionary. A limited set of prehospital data is gathered on each occurrence (Appendix 2). A contact person at each EMS agency (CARES liaison) ensures adherence to the criteria and provides routine communication with the project coordinator for issues, concerns, and questions. The data are submitted in one of the three ways: direct entry into the website database, exportation of electronic data from field software programs, or from an existing database. Hospitals receive notification to provide outcome data through an e-mail, which is automatically generated by the database. The five basic hospital level questions include emergency department outcome, TH treatment, hospital outcome, disposition location, and neurological status at the time of hospital discharge. The neurological status is categorized using the Cerebral Performance Category (CPC) scale as follows: 1 = good cerebral performance; 2 = moderate disability; 3 = severe cerebral disability; 4 = coma or vegetative state; and 5 = death. It is a CARES policy that only appropriately trained medical providers, such as a nurse or physician, makes the hospital discharge CPC scale determination, and each CARES site is provided with training materials to educate staff with regard to CPC scoring. In cases of inadequate documentation, the physician responsible for the patient discharge may be contacted for clarification.

The CARES staff reviews all records each month to identify any anomalies and immediately address all concerns. Data fidelity is assured through multilevel review, including software logic checks, and a data analyst examines each submitted report. If elements are missing from a report, an audit file is sent to the responsible site for clarification. Once the essential elements pass quality checks, individual identifiers are stripped from the record and the case is permanently entered into the registry database. For this study, the deidentified data, stored on a secure web server (Sansio Corporation, Minneapolis, MS), were exported to an excel file format (Microsoft Corporation, Redmond, WA) and electronically transferred to the principal investigator for analysis.

Statistical analysis

Summary statistics of medians and interquartile ranges, means and standard deviations, and proportions with 95% confidence intervals, when appropriate, were calculated for all eligible patients with and without TH. The outcome of interest was a CPC score indicating good cerebral performance or moderate disability (CPC = 1 or 2) versus a lower CPC score (3, 4, or 5) indicating severe cerebral disability, coma/vegetative state, or death, respectively. As per convention, we made the worse outcome the event, so odds ratios greater than 1 in the multivariate models indicate an association with a worse outcome.

For multivariate adjustment, a multilevel (i.e., hierarchical), mixed-effects logistic regression (MLR) model was used with hospitals treated as random effects (Rabe-Hesketh and Skrondal, 2008). This model allows for the possibility of serial correlation in outcomes among patients treated within the same hospital. With this model structure, we created several models. We created regression models using all

eligible patients and only included all mandatory fields deemed clinically relevant: age, gender, race, arrest location, witnessed arrest, TH given in the hospital (the main predictor of interest), TH given in the field, and the first documented rhythm category. Additional optional variables relating to chronic comorbidities, drugs used during resuscitation, and use of an impedance threshold device (ITD) were added as covariates in subsequent models. We performed no imputation and since these additional covariates were optional (and therefore missing from some patient records), the sample size in these regression models decreased. In the regression models, we also tested if an interaction effect was present with TH and the first documented rhythm category.

As an additional sensitivity analysis, we performed a propensity score matching analysis, where the propensity (probability) of having TH was modeled as the outcome using first the mandatory variables and then on all variables (comorbidities, drugs, ITD, prehospital time). Separate pro-

pensity scores were created for shockable and nonshockable patients (i.e., patients were directly matched on the rhythm category first) as a preliminary analysis showed that propensity matching on the entire dataset could not adequately match TH and No-TH patients by the first documented rhythm category. After matching the patients using a 5:1 greedy match algorithm, diagnostics were performed to ensure that the covariates (i.e., age, gender) were balanced between groups. Inferences done on the matched sample took the paired nature of the data into account.

Results

Population

There were 89,278 OHCA records available in the CARES database through December 31, 2012 representing a mixed dataset of prehospital and in-hospital cooling. After our predefined exclusions (Fig. 1), we were left with a final

FIG. 1. Exclusion criteria: There were 89,278 out-of-hospital cardiac arrest records available in the Cardiac Arrest Registry to Enhance Survival (CARES) database through December 31, 2012. After our predefined exclusions, we were left with a final sample size for this study of 6369 records for analysis.

*Prior to 01Nov2010, reporting of therapeutic hypothermia provision was not mandated.

**Presumed noncardiac etiologies include trauma, respiratory failure, drowning, electrocution, or other.

#Missing key data elements: age n=11, hypothermia provided n=214, hospital outcome n=345.

##Surrogate for likely poor baseline CPC potentially negatively biasing the hypothermia group.

%Surrogate for likely short arrest duration potentially positively biasing the control group.

sample size for this study of 6369 records (shockable = 2992 [47.0%]; asystole = 1657 [26.0%]; PEA = 1249 [19.6%]; other unspecified nonshockable = 471 [7.4%]) for analysis.

Stratified by TH status

Overall, more than half of the patients in this cohort were assigned to the TH group (3452 [54.2%] vs. 2917 [45.8%] in the No-TH group). Table 1A presents the key mandatory variables by treatment status for all included patients. The TH group was slightly younger, but TH usage did not differ by gender or race/ethnicity. The TH group had a higher proportion of witnessed cardiac arrests. The initiation of TH in the field was strongly associated with TH provision after hospital admission. As expected, patients with a shockable first documented rhythm were more likely to receive TH than those initially found with a nonshockable rhythm. There were no

differences between groups in the proportion of patients with a CPC score of 1 or 2, a CPC score of 3 or 4, and a CPC score of 5 (death), $p = 0.295$.

With respect to those variables that were optionally reported, patients with cancer, renal disease, and chronic heart disease comorbidities were less likely to receive TH treatment. (Table 1B) Regarding drugs given during resuscitation, there were significant differences between groups in the delivery of epinephrine, amiodarone, atropine, vasopressin, and lidocaine—with all but vasopressin being more prevalent in the TH group. Notably, patients with the longer times from ambulance dispatch to arrival to the ED were more likely to receive TH as well.

Unadjusted patient CPC status at the time of hospital discharge is presented in Figure 2. Overall, patients with a shockable first documented rhythm had less in-hospital mortality and more favorable neurological outcomes compared

TABLE 1A. RAW DIFFERENCES BETWEEN THERAPEUTIC HYPOTHERMIA PROVIDED AND NO-THERAPEUTIC HYPOTHERMIA PROVIDED FOR ALL PATIENTS (N=6369)

Variable	TH provided n = 3452 (54.2%)	No-TH provided n = 2917 (45.8%)	p-Value
Age (median, IQR)	62 (52, 72)	64 (54, 77)	<0.001
Age categories			<0.001
18–49	685 (19.84)	497 (17.04)	
50–59	824 (23.87)	627 (21.49)	
60–69	935 (27.09)	688 (23.59)	
70–79	607 (17.58)	565 (19.37)	
80–89	358 (10.37)	441 (15.12)	
90+	43 (1.25)	99 (3.39)	
% Female	1204 (34.88)	1073 (36.78)	0.114
Race			0.06
White	1574 (45.60)	1253 (42.96)	
Black	540 (15.64)	446 (15.29)	
Hispanic	231 (6.69)	192 (6.58)	
Asian/other	88 (2.55)	66 (2.26)	
Unknown race	1019 (29.52)	960 (32.91)	
Location of the event			0.069
Home	2491 (72.16)	2109 (72.30)	
Street	288 (8.34)	205 (7.03)	
Recreation location	108 (3.13)	117 (4.01)	
Public area/commercial area/jail/other	565 (16.37)	486 (16.66)	
Event known to be witnessed	2252 (65.24)	1810 (62.05)	0.008
Resuscitation initiated by (no CPR: n = 13)			0.348
Layman initiated CPR	1448 (41.95)	1237 (42.41)	
EMS initiated CPR	955 (27.67)	839 (28.76)	
First responder initiated CPR	1043 (30.21)	835 (28.63)	
AED used during resuscitation	191 (5.53)	196 (6.72)	0.048
Hypothermia initiated in the field (missing imputed to be none)	1688 (48.32)	628 (21.53)	<0.001
First documented rhythm			<0.001
Shockable (includes VFib, V Tach, and unknown shockable)	1851 (53.62)	1141 (39.12)	
Asystole	794 (23.00)	863 (29.59)	
Idioventricular/PEA	592 (17.15)	657 (22.52)	
Unknown unshockable rhythm	215 (6.23)	256 (8.78)	
Hospital outcome			0.295
CPC 1/2	1175 (34.04)	983 (33.70)	
CPC 3/4	208 (6.03)	151 (5.18)	
CPC 5	2069 (59.94)	1783 (61.12)	

TH, therapeutic hypothermia; PEA, pulseless electrical activity; EMS, Emergency Medical Service; CPC, Cerebral Performance Category; CPR, cardiopulmonary resuscitation.

TABLE 1B. RAW DIFFERENCES BETWEEN GROUPS FOR THE SUBSET WITH OPTIONAL FIELDS COMPLETED

Variable	TH provided n = 2255 (55.1%)	No-TH provided n = 1835 (44.9%)	p-Value
Comorbid conditions			
Diabetes	431 (19.11)	347 (18.91)	0.869
Cancer	105 (4.66)	131 (7.14)	0.001
Hypertension	602 (26.70)	537 (29.26)	0.068
Renal disease	103 (4.57)	115 (6.27)	0.016
Heart disease	655 (29.05)	589 (32.10)	0.035
Respiratory disease	273 (12.11)	227 (12.37)	0.798
Hyperlipidemia	111 (4.92)	100 (5.45)	0.448
Stroke	71 (3.15)	741 (3.87)	0.211
Variable	TH provided n = 2543 (55.5%)	No-TH provided n = 2040 (44.5%)	p-Value
Resuscitation drugs given			
Epinephrine	1998 (78.57)	1439 (70.54)	<0.001
Atropine	626 (24.62)	450 (22.06)	0.042
Bicarbonate	501 (19.70)	448 (21.96)	0.061
Amiodarone	583 (22.93)	295 (14.46)	<0.001
Vasopressin	402 (15.81)	383 (18.77)	0.008
Dextrose	114 (4.48)	95 (4.66)	0.779
Lidocaine	309 (12.15)	192 (9.41)	0.003
Variable	TH provided n = 2540 (55.6%)	No-TH provided n = 2031 (44.4%)	p-Value
Impedence threshold device used	673 (26.5)	431 (21.2)	<0.001
Variable	TH provided n = 2749 (50.7%)	No-TH provided n = 2040 (49.3%)	p-Value
Time from ambulance dispatch to ED arrival (minutes); groups represent quintiles of equal size			<0.001
17:10 to 28:26	483 (17.57)	602 (22.48)	
28:28 to 34:59	505 (18.37)	514 (19.19)	
35:00 to 41:17	583 (21.21)	567 (21.17)	
41:18 to 50:40	585 (21.28)	502 (18.75)	
50:41 or Later	593 (21.57)	493 (18.41)	

with those who were found to be in a nonshockable rhythm on EMS arrival. Across the rhythm categories, those with TH had either similar proportions of patients with good or moderate disability CPC status as those with No-TH or had statistically significantly fewer patients with this outcome.

At the hospital level, the proportion of patients treated with TH varied widely across institutions as indicated by the histogram in Figure 3. This analysis excluded any hospital that contributed fewer than 10 eligible patients so as to not distort the hospital-level TH rate. Whereas the average proportion of patients treated with TH in the cohort exceeded 50%, the range was quite broad with some hospitals rarely using TH, while others provide it to the vast majority of their patients. Moreover, at the hospital level, the correlation between the TH rate and percent of patients with nonshockable rhythm was modest, $r=0.30$, $p<0.001$.

Multivariate results are presented in Table 2 and the multivariate sensitivity analyses are given in Table 3. The multilevel (i.e., hierarchical), MLR model in Table 2 shows that TH for all patients, after adjusting only for the mandatory

fields, was significantly associated with a worse neurological outcome (CPC score of 3, 4, or 5—severe cerebral disability, coma, or death). The model includes an interaction term with the first documented rhythm category and for the unknown nonshockable rhythm category; the interaction was significant (interaction term odds ratio = 2.18). This means that the main effect odds ratio for TH of 1.35 is not constant, but is higher (by a factor of 2.177) when the rhythm category is unknown nonshockable (i.e., these patients do worse than expected). A likelihood ratio test for this model compared with a logistic regression model that did not take hospital-level effects into account was significant ($p<0.001$) indicating that the hospital for which the patient was treated was significantly associated with outcome.

Table 2 presents the results for all patients. Table 3 presents the multivariate results applied to the subsets of shockable and nonshockable patients. In this study, we see that when we use all variables (i.e., the variables in Table 2 plus comorbidities, drugs, and time from ambulance dispatch to ED arrival as shown in Table 1B), TH appears nonsignificant in all shockable patients and in the propensity

FIG. 2. Unadjusted patient Cerebral Performance Category results at the time of hospital discharge.

matched sample of shockable patients. The propensity matched sample of nonshockable patients using all variables also found TH to have no significant relationship with outcome. In contrast, the propensity-matched samples that only adjusted for the mandatory variables (in the last two rows of Table 3) showed that TH was associated with significantly worse outcomes for both shockable and nonshockable patients. Thus, the propensity-matched results

mirrored the corresponding regression model results that used the same variables.

Discussion

Comparative Effectiveness Research (CER) examines the real-world outcomes of two or more treatment options for a given medical condition—as opposed to efficacy, which is

FIG. 3. Histogram of the percentage of patients treated with therapeutic hypothermia (TH) across institutions—the percentage of patients receiving TH varied considerably by hospital. Some hospitals rarely provided TH and others almost always. Overall, about half the patients received TH, but at the hospital level, the rate of TH was not consistently 50% and it varied from very low (<10%) to very high (>90%).

TABLE 2. MULTIVARIATE RESULTS WITH AN INTERACTION TERM ($N=6369$)

<i>Variable</i>	<i>Odds ratio</i>	<i>95% confidence intervals</i>	<i>p > z </i>
Therapeutic hypothermia	1.353	(1.134–1.616)	0.001
Age categories			
18–49	1		
50–59	1.228	(1.014–1.488)	0.036
60–69	1.774	(1.468–2.144)	<0.001
70–79	2.723	(2.199–3.371)	<0.001
80–89	4.14	(3.194–5.367)	<0.001
90+	5.536	(3.103–9.879)	<0.001
Female gender	1.404	(1.219–1.616)	<0.001
Race			
White	1		
Black	1.291	(1.049–1.590)	0.016
Hispanic	1.53	(1.110–2.110)	0.009
Asian/other	0.966	(0.618–1.508)	0.879
Unknown race	1.069	(0.903–1.267)	0.437
Location of the event			
Home	1		
Street	0.655	(0.522–0.823)	<0.001
Recreation location	0.288	(0.201–0.411)	<0.001
Public area/commercial area/jail/other	0.524	(0.443–0.620)	<0.001
Event known to be witnessed (yes = 1)	0.678	(0.587–0.784)	<0.001
Resuscitation initiated by			
EMS initiated CPR	1		
Layman initiated CPR	0.75	(0.635–0.886)	0.001
First responder initiated CPR	0.9	(0.749–1.081)	0.26
Hypothermia initiated in the field (yes = 1)	1.194	(0.019–1.400)	0.028
First documented rhythm			
Shockable (includes VFib, V Tach, and unknown shockable)	1		
Asystole	13.219	(9.763–17.899)	<0.001
Idioventricular/PEA	4.398	(3.421–5.655)	<0.001
Unknown unshockable rhythm	1.757	(1.290–2.393)	<0.001
TH × rhythm category			
TH × shockable	1		
TH × asystole	0.942	(0.615–1.444)	0.784
TH × PEA	1.163	(0.810–1.672)	0.413
TH × unknown unshockable	2.177	(1.360–3.485)	0.001

TABLE 3. MULTIVARIATE SENSITIVITY ANALYSES

<i>Group</i>	<i>Odds ratio for TH; higher odds ratio = worse outcome</i>	<i>95% confidence intervals</i>	<i>p-Value</i>	<i>Sample size</i>
Using all variables				
Greedy matched	Shockable only	0.921	(0.683, 1.244)	0.593 363 matched pairs
No matching, but all available variables in a multilevel mixed-effects logistic regression	Shockable only	1.11	(0.849, 1.451)	0.447 1726 patients
Greedy matched	Nonshockable only	1.017	(0.710, 1.457)	0.927 425 matched pairs
No matching, but all available variables in a multilevel mixed-effects logistic regression	Nonshockable only	1.444	(1.039, 2.006)	0.029 1830 patients
Using all patients on mandatory variables				
Multilevel mixed-effects logistic regression	All patients	1.353	(1.134–1.616)	0.001 6369 (note an interaction term is present)
Greedy matched	Shockable only	1.313	(1.056, 1.630)	0.014 681 matched pairs
Greedy matched	Nonshockable only	1.746	(1.293, 2.358)	<0.001 741 matched pairs

the ideal therapeutic effect under rigidly controlled conditions as in a randomized controlled clinical trial. CER research, such as ours, always has a selection bias (i.e., the treatment choice is not randomly assigned), which must be attenuated with multivariate methods that adjust for confounding variables. CER research also tends to have more data collection errors or missing data due to the real-world setting and often, important confounders are simply not recorded or available for analysis. In this study, done to determine the effectiveness of TH compared with No-TH in OHCA survivors with an emphasis on subgroups of those with a nonshockable first documented rhythm, we found that after multivariate adjustment, TH had either no association with neurological status at hospital discharge or that TH was actually associated with worse neurological outcomes, particularly in patients with a nonshockable first documented rhythm.

These results differ from a recent systematic review and meta-analysis, which once again reaffirmed that induced mild TH improves survival and neurological outcomes after cardiac arrest resuscitation (Arrich *et al.*, 2012). However, systematic review and meta-analysis included only randomized and quasirandomized controlled trials and so is more an assessment of TH efficacy. In addition, the total number of patients in the five included studies was small (253 treatment patients, 226 controls) with over 70% of the TH patients and more than 75% of the controls originating from the two landmark randomized control trials that are now over 10 years old. Our study is an examination of the real-world outcomes between patients treated with TH and those not treated, and included over 6000 patients and so is more a reflection of current day treatment effectiveness subject to the limitations intrinsic to any CER study.

Our study is unique in that, it is the first longitudinally collected and validated single source data analysis of TH treatment large enough to stratify outcomes by first documented rhythm subgroups. Further, the data included key predictive resuscitation variables for inclusion in our modeling to better explain the raw group differences. Because this study is not a random trial and the TH was not randomly assigned (i.e., it appeared that more acutely ill patients were given this treatment), our reported multivariate results are more definitive than the raw results. However, since the CARES dataset has important clinical factors to be optionally reported, we are faced with two types of models. The first are models with the largest sample size possible (i.e., only mandatory variables), while the second adjusts for all variables and examines only subsets of patients by rhythm category with this reported data. The former show us how TH does in a more broadly defined population of patients. The latter have the advantage of adjusting for more confounders and with propensity matching; we are getting samples on No-TH patients most like their TH counterparts. Whereas these latter models are less generalizable to all OHCA patients, they are also less biased to unmeasured confounding and the sample sizes are still large and much larger than previous studies in the literature.

With our propensity-matched models using all variables, we saw that TH had no association with outcome for either shockable or nonshockable patients. When we did not adjust for all variables, either using the multilevel logistic regression model on all patients or stratifying by rhythm with propensity

matching, we saw that TH was associated with a worse outcome. Since our result differed when more covariates were added to the models, we feel that the models that did not adjust for comorbidities, drugs, and prehospital time are biased. Nevertheless, in the model in Table 2, we did observe a significant interaction effect indicating that TH was associated with a worse outcome than expected for patients with unknown nonshockable rhythms. This interaction odds ratio was similar in magnitude ($OR = 1.975$), but borderline nonsignificant ($p = 0.055$) when we examined these factors in a model that adjusted for all variables, but we note that interactions require a much larger sample size to be adequately powered (usually four times the sample size as main effects). Thus, our regression results show that, with shockable as the referent, patients with a nonshockable first documented rhythm as a whole have much worse outcomes when provided TH, and the effect is not constant across the nonshockable rhythm subcategories.

The utilization of TH varied widely across participating hospitals, and its use was not strongly correlated with the percent of patients at each with shockable rhythms. Our results show that getting TH is strongly dependent on the admitting hospital type, which suggests that endorsed treatment guidelines for the care of resuscitated OHCA patients are not consistently followed nationwide.

We stress that our results should not be interpreted as evidence that TH is not beneficial, but merely that when applied indiscriminately across a large heterogeneous cohort of OHCA survivors, as in routine clinical practice, its contribution to patient outcomes is diluted and evidence of a measurable effect is lost. Our findings are important because as the effectiveness of the treatment diminishes, the number needed to treat (estimated to be six per life saved) increases substantially (Holzer *et al.*, 2005), and the cost-effectiveness of the therapy (initially calculated as \$47,168 per quality-adjusted life year) may be greater than expected (Merchant *et al.*, 2009).

Study limitations

The use of registry data has inherent limitations. The most important of which, for appropriately interpreting our study results, is various sources of bias (i.e., selection and misclassification bias). There was no independent verification of the appropriateness of point-of-care inclusion and exclusion decisions or classification accuracy.

As with all retrospective analyses, unmeasured confounders can generate unexpected results. We must stress that CARES is structured to collect binary information on the initiation of TH (i.e., cooled? yes or no) and does not take into account many of the confounding variables related to implementation and time to initiation. As such, no details are available on pre-existing advanced directive or withdrawal of care once initiated; pretreatment neurological status; hemodynamic stability or management during treatment; or the timing, quality, or duration of treatment (i.e., time to target temperature or cooling/rewarming procedures).

In addition, the time from arrest to first documented rhythm is challenging to capture and is not a component of the registry. It is possible that group differences in neurological outcome could be due, in part, to the duration of ischemia before attempted resuscitation. Furthermore, we had no data on quality of resuscitation efforts or time to

ROSC. In addition, the initial ECG rhythm classification was not independently confirmed. However, there is no reason to believe that a systematic bias exists in the way rhythm categories were recorded. Finally, the CARES database is limited in the number of comorbidities it tracks and so earlier conditions not collected, such as morbid obesity and their confounding effect on mortality or CPC scores, are unknown.

In terms of outcome, we acknowledge that patients' long-term (30-day or 90-day) neurological status is unknown since CPC scores are only recorded at the time of hospital discharge. Therefore, any neurological improvement occurring beyond this time point (Raina *et al.*, 2008) would not be captured. However, the CPC at hospital discharge has recently been shown to be a useful surrogate measure of long-term quality survival after cardiac arrest resuscitation (Phelps *et al.*, 2013).

Future studies should begin by addressing these limitations, and we encourage a multicenter randomized clinical trial to specifically examine the effect of TH on patients after successful cardiac arrest resuscitation with a nonshockable first documented rhythm.

Conclusion

Highlighting our limitations, we conclude that when TH is indiscriminately provided to a large population of OHCA survivors with a nonshockable first documented rhythm, evidence for its effectiveness is diminished. We emphasize that TH may still be effective, particularly for certain patient subsets, but perhaps, more uniform and rigid guidelines for application are needed to assure more appropriate application, and a randomized controlled clinical trial on nonshockable patients appears warranted.

Acknowledgments

The Cardiac Arrest Registry to Enhance Survival (CARES) is funded by grant support from the American Red Cross, the Medtronic Foundation Heart Rescue Project, the American Heart Association, and the Zoll Corporation. The project was supported by the National Center for Research Resources, the National Center for Advancing Translational Sciences, and the National Institutes of Health, through grant number UL1 RR025752. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. The data analysis was funded by a project grant from the Laerdal Foundation for Acute Care Medicine.

Disclosure Statement

All authors declare that no competing financial interests exist.

References

Arrich J, Holzer M, Havel C, Mullner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev* 2012;9: CD004128.

Cummins RO, Chamberlain DA, Abramson NS, *et al.* Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A state-

ment for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991;84: 960–975.

Dumas F, Grimaldi D, Zuber B, *et al.* Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. *Circulation* 2011; 123:877–886.

ECC Committee, Subcommittees and Task Forces of the American Heart Association. 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2005;112:IV1–203.

Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. *Lancet* 1994;343: 1055–1059.

Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Mullner M. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* 2005;33:414–418.

Jacobs I, Nadkarni V, Bahr J, *et al.* Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Councils of Southern Africa). *Circulation* 2004;110:3385–3397.

Kim YM, Yim HW, Jeong SH, Klem ML, Callaway CW. Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms? A systematic review and meta-analysis of randomized and non-randomized studies. *Resuscitation* 2012;83:188–196.

Kory P, Fukunaga M, Mathew JP, *et al.* Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. *Neurocrit Care* 2012;16:406–412.

Lundbye JB, Rai M, Ramu B, *et al.* Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. *Resuscitation* 2012;83:202–207.

McNally B, Stokes A, Crouch A, Kellermann AL. CARES: cardiac arrest registry to enhance survival. *Ann Emerg Med* 2009;54:674–683.e2.

Merchant RM, Becker LB, Abella BS, Asch DA, Groeneveld PW. Cost-effectiveness of therapeutic hypothermia after cardiac arrest. *Circ Cardiovasc Qual Outcomes* 2009;2: 421–428.

Peberdy MA, Callaway CW, Neumar RW, *et al.* Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010;122:S768–S786.

Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. *Crit Care Med* 2013;41:1252–1257.

Rabe-Hesketh S, Skrondal A. *Multilevel and Longitudinal Modeling Using Stata*. 2nd ed. College Station, TX: Stata Press, 2008.

- Raina KD, Callaway C, Rittenberger JC, Holm MB. Neurological and functional status following cardiac arrest: method and tool utility. *Resuscitation* 2008;79:249–256.
- Soga T, Nagao K, Sawano H, *et al.* Neurological benefit of therapeutic hypothermia following return of spontaneous circulation for out-of-hospital non-shockable cardiac arrest. *Circ J* 2012;76:2579–2585.
- Storm C, Nee J, Roser M, Jorres A, Hasper D. Mild hypothermia treatment in patients resuscitated from non-shockable cardiac arrest. *Emerg Med J* 2012;29:100–103.
- Testori C, Sterz F, Behringer W, *et al.* Mild therapeutic hypothermia is associated with favourable outcome in patients after cardiac arrest with non-shockable rhythms. *Resuscitation* 2011;82:1162–1167.
- Walters JH, Morley PT, Nolan JP. The role of hypothermia in post-cardiac arrest patients with return of spontaneous

circulation: a systematic review. *Resuscitation* 2011;508–516.

Williams GR Jr., Spencer FC. The clinical use of hypothermia following cardiac arrest. *Ann Surg* 1958;148:462–468.

Address correspondence to:
 Timothy J. Mader, MD
 Department of Emergency Medicine
 Baystate Medical Center
 Tufts University School of Medicine
 759 Chestnut St.
 Springfield, MA 01199

E-mail: timothy.mader@baystatehealth.org

Appendix

APPENDIX 1: Site Map

<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="width: 30%;"></div> <div style="width: 40%; text-align: center;"> <h2 style="margin: 0;">Cardiac Arrest Registry</h2> </div> <div style="width: 20%; text-align: center;"> </div> </div>			
Part A : Demographic Information			
1 - Street Address (Where Arrest Occurred)			
2 - City		3 - State	4 - Zip Code
5 - First Name		6 - Last Name	
7 - Age	9 - Date of Birth	10 - Gender	11 - Race/Ethnicity
Part B : Run Information			
14 - Date of Arrest		15 - Incident #	
First Responding Agency			
16 - Fire/First Responder		17 - Destination Hospital	
Part C : Arrest Information			
18 - Location Type	19 - Arrest Witnessed	20 - Arrest After Arrival of 911 Responder	21 - Presumed Cardiac Arrest Etiology
Resuscitation Information			
22 - Resuscitation attempted by 911 Responder (or AED shock given prior to EMS arrival)	23 - Who Initiated CPR	24 - Type of Bystander CPR Provided	
25 - Was an AED applied prior to EMS arrival	26 - Who First Applied the AED	27 - Who First Defibrillated the Patient	
First Cardiac Arrest Rhythm of Patient and ROSC Information			
30 - First Arrest Rhythm of Patient	31 - Sustained ROSC (20 consecutive minutes) or present at end of EMS Care	32 - Was hypothermia care provided in the field	33 - End of Event
Part E: Hospital Section			
46 - ER Outcome	48 - Hospital Outcome	49 - Discharge from the Hospital	
47 - Was hypothermia care initiated or continued in the hospital	50 - Neurological Outcome At Discharge From Hospital	51 - Discharge from the Hospital	
General Comments			