The Utility of Therapeutic Hypothermia for Post–Cardiac Arrest Syndrome Patients With an Initial Nonshockable Rhythm

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Background—Therapeutic hypothermia (TH) attenuates reperfusion injury in comatose survivors of cardiac arrest. The utility of TH in patients with nonshockable initial rhythms has not been widely accepted. We sought to determine whether TH improved neurological outcome and survival in postarrest patients with nonshockable rhythms.

Methods and Results—We identified 519 patients after in- and out-of-hospital cardiac arrest with nonshockable initial rhythms from the Penn Alliance for Therapeutic Hypothermia (PATH) registry between 2000 and 2013. Propensity score matching was used. Patient and arrest characteristics used to estimate the propensity to receive TH were age, sex, location of arrest, witnessed arrest, and duration of arrest. To determine the association between TH and outcomes, we created 2 multivariable logistic models controlling for confounders. Of 201 propensity score–matched pairs, mean age was 63±17 years, 51% were male, and 60% had an initial rhythm of pulseless electric activity. Survival to hospital discharge was greater in patients who received TH (17.6% versus 28.9%; P<0.01), as was a discharge Cerebral Performance Category of 1 to 2 (13.7% versus 21.4%; P=0.04). In adjusted analyses, patients who received TH were more likely to survive (odds ratio, 2.8; 95% confidence interval, 1.6–4.7) and to have better neurological outcome (odds ratio, 3.5; 95% confidence interval, 1.8–6.6) than those that did not receive TH.

Conclusions—Using propensity score matching, we found that patients with nonshockable initial rhythms treated with TH had better survival and neurological outcome at hospital discharge than those who did not receive TH. Our findings further support the use of TH in patients with initial nonshockable arrest rhythms.

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Key words: cardiopulmonary resuscitation ■ heart arrest ■ hypothermia, induced ■ resuscitation

Therapeutic hypothermia (TH) or targeted temperature management has been widely accepted as the only known therapy to impart neuroprotection to the post–cardiac arrest patient with anoxic injury resulting in coma after the return of spontaneous circulation. The landmark studies that documented this phenomenon were performed on comatose patients after an out-of-hospital cardiac arrest (OHCA) with an initial shockable rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT).1,2 The incidence of initial shockable arrest rhythms, specifically VF and pVT, has been declining over recent years, whereas the incidence of all cardiac arrest continues to be estimated at 540,000 individuals in the United States alone.3,4 This phenomenon results in a larger proportion of individuals who have had a cardiac arrest because of a nonshockable initial rhythm and who might benefit from aggressive postresuscitation care. Despite this increasing burden of disease related to nonshockable arrests, randomized controlled trials to examine the utility of TH in patients with nonshockable rhythms (pulseless electric activity [PEA] and asystole) have not been completed, and available observational studies have yielded conflicting results. Nielsen et al5 presented the only randomized controlled trial in post–cardiac arrest care that included nonshockable initial rhythms with the objective to compare targeted temperature management at 33°C versus 36°C; however, the question of benefit for patients with initial nonshockable rhythms was not specifically addressed and the study did not include a control group that did not receive active temperature management.

Multiple retrospective cohort studies have examined the association between TH and neurological outcomes in patients who have a cardiac arrest with nonshockable rhythms; however, the results have been varied, thus reinforcing the controversy surrounding the use of TH in this cohort of patients. Specifically, the association between TH use in the cohort...
of patients with nonshockable rhythms and good neurologi-
cal outcome has yielded both a positive association,6 and no
effect, as well,7 resulting in a recent decision by the American
Heart Association to render TH a level I recommendation
in patients who have return of spontaneous circulation after
cardiac arrest with an initial rhythm of PEA or asystole.8
Nonetheless, further practical evidence to support this recom-
mendation is sought.

We sought to further explore the association between TH
and neurological outcomes in patients with an initial non-
shockable rhythm by simulating a randomized controlled trial
using a propensity score to create our treatment and control
groups.9 We hypothesized that patients with a nonshockable
rhythm treated with TH would have better neurological out-
comes (defined as a Cerebral Performance Category [CPC]
of 1 or 2) at hospital discharge versus their propensity score–
matched counterparts who did not receive TH.

Methods

Study Design and Setting
This is a retrospective cohort study utilizing data from the Penn Alliance
for Therapeutic Hypothermia (PATH) Registry. The PATH registry was
created as a national, on-line repository for patient data from multiple
centers using TH in the management of post–cardiac arrest patients.
This was a multicenter study evaluating patient data from 16 institu-
tions that currently contribute to the PATH registry. This collaborative
study was approved by the University of Pennsylvania Institutional
Review Board, and each center obtained site-specific institutional
review board approval before their participation in the PATH registry.

Study Cohort
Patients enrolled in this study were ≥18 year of age, had experienced
either an in-hospital or nontraumatic OHCA with an initial nonshock-
able cardiac arrest rhythm of either PEA or asystole. All patients were
comatose after the return of spontaneous circulation and, therefore,
eligible for TH. Patients in this cohort did not have an active Do Not
Resuscitate order.

Treatment
Patients either underwent TH according to the respective institutional
protocols (all with standard goal temperatures of 32°C to 34°C in
accordance with American Heart Association guidelines) or received
standard postarrest care without the application of TH.

Data Collection
Patient-specific data were added to the online registry by trained data
abstractors at each contributing site. Demographic data were obtained
for each subject, including age at arrest, sex, and race. Arrest character-
istics were collected including the location of arrest (in-hospital versus
out-of-hospital), initial nonshockable rhythm (asystole versus PEA),
witnessed arrest, administration of bystander cardiopulmonary resus-
citation, and finally the duration of arrest. Duration of arrest is defined
as the time from prehospital notification for OHCA, or activation of
a code call for in-hospital cardiac arrest until the return of spontane-
cous circulation, respectively. The primary outcome was neurological
outcome at hospital discharge as characterized by CPC dichotomized
into good outcome (CPC 1–2) or poor outcome (CPC 3–5),9–11 and a
secondary outcome analyzed was survival to hospital discharge.

Statistical Analysis
We described the baseline characteristics of the study population by
using frequencies for categorical variables and means with standard
deviations for continuous variables. Comparisons for continuous data
were made via the Student t tests or Mann-Whitney U tests, and χ2
testing was applied to categorical data.

To control for confounding by indication, we used a propensity
score matching method to determine a score for each patient’s
propensity to receive TH.12,13 A propensity score, defined as the
conditional probability of being treated given the covariates, was
created by using a nonparsimonious logistic regression model
accounting for patient and arrest characteristics identified a priori
based on previous literature.14 With the use of a specialized sta-
tistical package (psmatch2), scores were created and cases were
matched on the propensity score in a 1:1 block using nearest-
neighbor matching algorithm with replacement. Replacement
allows for a unit (patient) to be selected more than once, thus
reducing the distance between the matched units and allowing
each pair to be matched to its closest neighbor. After deriving
the propensity score and completing the matched pairs, post-
estimation diagnostics were applied to ensure balance between
the 2 cohorts, that use of the propensity score matching led to
a reduction of bias (as opposed to not using a propensity score
match), and to identify outliers for exclusion to avoid undue bias.
Utilizing the propensity score–matched cohort, we created mul-
tivariable conditional logistic regression models to determine
the association between (1) TH and neurological outcome (CPC
dichotomized into good [CPC 1 and 2] and poor [CPC 3–5]) and
(2) TH and survival to hospital discharge, accounting for relevant
confounding variables as identified on univariate analysis. All
analysis was completed using basic statistical software (STATA
v.12, Statacorp, College Station, TX). For propensity score deri-
vation and matching, we used the STATA program psmatch2.15

Results
Between 2000 and 2013, 519 patients in the PATH registry
had a cardiac arrest because of a nonshockable initial rhythm
(PEA or asystole), had return of spontaneous circulation, and
were comatose at hospital admission. Of the entire cohort
of patients, 50.5% (262) of comatose survivors underwent
TH according to their respective hospital protocols. Table 1
reports the demographic and arrest characteristics for patients
who underwent TH and those in the standard care (no TH)
group. Of note, patients who underwent TH were younger
(62 versus 69 years of age, P<0.001), had longer durations of
arrest (23 versus 13 minutes, P<0.001), and had a higher inci-
dence of asystole as their primary rhythm (45% versus 35%,
P<0.001). Patients who underwent TH were more frequently
patients who had had an OHCA (82% versus 39%, P<0.001),
which most likely reflects a preference for 1 aspect of the
patient population studied in the landmark trials of 2002.12
The median time to hospital discharge varied and was highest
(19.0 days, [Q1,Q3] 13.0, 25.7 days) in the cohort of patients
who survived after TH and lowest in the cohort that died with-
out TH (0.9 days, [Q1,Q3] 0.2, 2.3 days).

Propensity scores were calculated based on the factors
influencing the likelihood of receiving TH: age, sex, initial
rhythm, witnessed arrest, duration of arrest, and location of
arrest.14 After generating propensity scores, 291 patients
were matched to form 201 pairs. One outlier patient was
excluded after postestimation testing showed that his/her
inclusion caused bias. Figure represents the distribution of
patients enrolled over time (calendar year) for the propen-
sity score–matched cohort. Table 2 describes the propensity
score–matched cohort, where there is no statistical difference
between the demographic and arrest characteristics of the TH
and standard-care cohorts.
In univariate analysis, we found that female sex (odds ratio [OR], 0.50; 95% confidence interval [CI], 0.28–0.88), PEA as the initial rhythm (OR, 2.04; 95% CI, 1.14–3.66), witnessed arrest (OR, 3.7; 95% CI, 1.78–7.90) and duration of arrest in minutes (OR, 0.94; 95% CI, 0.92–0.96) are independently associated with neurological outcome. In the propensity-matched cohort, 29% of patients who underwent TH survived to hospital discharge versus 15% that did not receive hypothermia ($\textit{P}=0.001$). In this same population, 21% of patients who underwent TH survived to hospital discharge with a CPC 1 or 2 in comparison with only 10% in the cohort who did not receive hypothermia ($\textit{P}=0.001$). In this same population, 21% of patients who underwent TH survived to hospital discharge with a CPC 1 or 2 in comparison with only 10% in the cohort who did not receive TH ($\textit{P}=0.003$). In multivariate analysis (Table 3), we found that TH was associated with improved neurological outcomes for patients who had a cardiac arrest attributable to a nonshockable rhythm 3.5-fold (95% CI, 1.8–6.6). In addition, we found that TH was associated with improved survival to hospital discharge in this same cohort with an OR of 2.8 (95% CI, 1.6–4.7).

We completed a subgroup analysis of in-hospital versus out-of-hospital cardiac arrest, given that the survival rate for the 2 cohorts is markedly different.16,17 The propensity score-matched cohort was separated by location of arrest, and novel propensity scores were generated for each cohort using the same variables as previously defined. After matching, 159 pairs of OHCA patients and 42 pairs of in-hospital cardiac arrest patients were analyzed. Using multivariable logistic regression to analyze these 2 subgroups separately (Table 3), we found that, regardless of the location of the arrest, patients who underwent TH were more likely to survive to hospital discharge neurologically intact (OHCA: OR, 2.1; 95% CI, 1.01–4.36; in-hospital cardiac arrest: OR, 4.23; 95% CI, 1.20–14.94). Despite the location of the arrest, patients with initial nonshockable arrest rhythms benefited from treatment with TH. When completing a subgroup analysis of in-hospital versus out-of-hospital arrest, patients who were treated with TH uniformly had better neurological outcomes than those who were not. This study is the first study to address the specific question of the utility of TH in this patient population by using advanced statistical methodology to control for confounding by indication and to define a study population that is statistically uniform between the treatment cohort and standard care arm. These results lend support to a broadening of indications for TH in comatose postarrest patients with initial nonshockable rhythms.

The randomized trials of 2002 established precedence for the use of TH in post–cardiac arrest care. These 2 studies focused primarily on patients who had an OHCA attributable to VF or pVT.1,2 This fact has led to much controversy in recent years. Many clinicians have expanded the use of TH to comatose patients regardless of initial rhythm (VF, pVT, PEA, asystole) or location of arrest (out-of-hospital versus in-hospital), searching for a clinical strategy to improve outcomes in this critically ill patient population. Simultaneously, many clinicians have questioned the utility of TH in patients who have an arrest because of a rhythm that is not VF or pVT, citing the fact that the evidence to support TH use did not arise from a study of this population specifically. Since that time, investigators have sought to evaluate the use of TH in all rhythms via

### Table 1. Patient Demographics and Arrest Characteristics for Patients Treated With Standard Postarrest Care (That Excluded TH) Versus Those Treated With TH

<table>
<thead>
<tr>
<th></th>
<th>Standard Care (No TH) (n=257)</th>
<th>Treated with TH (n=262)</th>
<th>$\textit{P}$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (Q1, Q3)</td>
<td>69 (55.5, 80)</td>
<td>62 (49, 73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of arrest, min (Q1, Q3)</td>
<td>13 (8, 28)</td>
<td>23 (14, 36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>127 (49)</td>
<td>143 (55)</td>
<td>0.239</td>
</tr>
<tr>
<td>OHCA, n (%)</td>
<td>100 (39)</td>
<td>216 (82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Witnessed arrest, n (%)†</td>
<td>215 (84)</td>
<td>182 (70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial rhythm, asystole, n (%)</td>
<td>89 (35)</td>
<td>119 (45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OHCA indicates out-of-hospital cardiac arrest; and TH, therapeutic hypothermia.

* $\textit{P}$ values derived by comparing patient groups with Student $t$ test or Mann-Whitney $U$ test for continuous variables and $\chi^2$ for categorical variables.

†Twelve patients in this cohort had missing data for witnessed arrest.

### Discussion

The findings suggest that TH is a beneficial treatment for comatose postarrest patients when the initial rhythm was either PEA or asystole. Through using propensity score matching in a retrospective registry of post–cardiac arrest patients with nonshockable initial rhythms (both PEA and asystole), patients who underwent TH had increased rates of survival with good neurological outcome (OR, 3.5; 95% CI,1.8–6.6) versus those who did not receive TH. In addition,
retrospective single-institution studies and large-registry studies, with the majority of those not endorsing TH in patients with nonshockable rhythms continuing to call for a randomized controlled trial to prove efficacy. Clinical investigators are reticent to design such a trial, because standard of care in many cardiac arrest centers nationwide uses TH in patients with all presenting rhythms who achieve return of spontaneous circulation. This unfortunately creates a conundrum where clinicians are divided among those who continue to call for more evidence and those who find it ethically questionable to randomly assign patients into a study where patients may have care withheld that they would have received were they to not enroll in the study. This led our study group to look to advanced statistical methodology to further investigate this topic.

Previous studies have found variability in the association between TH and neurological survival in patients who have cardiac arrest because of nonshockable rhythms. In 1 large retrospective registry study, investigators found that TH was not associated with good neurological outcome in patients with an initial nonshockable rhythm (OR, 0.71; 95% CI, 0.37–1.36). This study used multivariable logistic regression to determine the association between initial rhythm and the use of TH for all post–cardiac arrest patients admitted to a single tertiary care institution in Paris, France from 2000 to 2009. In contrast, a separate retrospective study conducted by Lundbye et al determined that patients with initial nonshockable rhythms treated with TH had improved outcomes in comparison with a historical cohort of cardiac arrest patients treated before the implementation of a TH protocol. That study, like our result, supports the use of TH in patients with initial nonshockable rhythms. The authors used data from a single institution with a total of 100 patients (52 in the TH cohort, 48 in the historical cohort) enrolled. Despite the small sample size, on adjusted analysis, patients treated with TH had significantly improved chance of neurological recovery versus the historical cohort that did not receive TH (OR, 5.65; 95% CI, 1.66–19.23). Both aforementioned studies were observational in nature; therefore, it is plausible that provider bias and confounding by indication may have affected which patients received TH. In our study, by matching based on propensity score, the control arm (no TH) and the interventional arm (treated with TH) were statistically uniform. This methodology was used to reduce the role that selection bias may have on the final outcome, survival to hospital discharge neurologically intact.

Patients with initial nonshockable rhythms were not included in the study design of the landmark trials of 2002. However, in 2013 Nielsen et al published a large multicenter RCT of OHCA patients with all initial rhythms treated with targeted temperature management at different maintenance temperatures (33°C versus 36°C). Although not a primary study question, the authors did report a subgroup analysis where they found an unadjusted overall survival of 16.1% for patients with initial nonshockable rhythms. In comparison, this survival rate is considerably higher than some previously reported for patients with initial nonshockable rhythms ranging from 4.6% to 10%, but less than that reported in a large database of TH patients, The Hypothermia Network, where 6-month survival for PEA patients was 23% and, for asystole patients, 6-month survival was 27%.

Despite established guidelines for the use of TH in patients who have cardiac arrest, adoption of this practice has been low, especially for in-hospital cardiac arrest patients and patients who have a cardiac arrest with initial nonshockable rhythms. This finding is surely influenced by prior guidelines that did not heavily support TH in this cohort; however, with guideline change, it is feasible this trend may change. Undoubtedly, both subpopulations of patients require further investigation to increase our scientific knowledge of efficacy and continue to improve clinical outcome. Our findings provide further support for the use of

Table 2. Propensity Score–Matched Cohort Demographics and Arrest Characteristics

<table>
<thead>
<tr>
<th>Status at Hospital Discharge</th>
<th>Standard Care (No TH) (n=201)</th>
<th>Treated With TH (n=201)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (Q1, Q3)</td>
<td>62 (50, 70)</td>
<td>60 (48, 72)</td>
<td>0.49</td>
</tr>
<tr>
<td>Duration of arrest, min (Q1, Q3)</td>
<td>25 (9, 36)</td>
<td>23 (14, 36)</td>
<td>0.63</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>113 (56)</td>
<td>108 (54)</td>
<td>0.62</td>
</tr>
<tr>
<td>OHCA, n (%)</td>
<td>163 (81)</td>
<td>159 (79)</td>
<td>0.62</td>
</tr>
<tr>
<td>Witnessed arrest, n (%)†</td>
<td>147 (73)</td>
<td>137 (68)</td>
<td>0.38</td>
</tr>
<tr>
<td>Initial rhythm, asystole, n (%)</td>
<td>77 (38)</td>
<td>91 (45)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

OHCA indicates out-of-hospital cardiac arrest; and TH, therapeutic hypothermia.
*P values derived by comparing patient groups with Mann-Whitney U test for continuous variables and the χ² test for categorical variables.
†Four patients in this cohort had missing data for witnessed arrest.

Table 3. Outcomes for the Multivariate Analysis of the Propensity–Matched Cohort of Patients Treated With and Without Therapeutic Hypothermia

<table>
<thead>
<tr>
<th>Status at Hospital Discharge</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td>2.8 (1.6–4.7)</td>
</tr>
<tr>
<td>IHCA</td>
<td>2.2 (0.8–6.2)</td>
</tr>
<tr>
<td>OHCA</td>
<td>3.1 (1.6–5.8)</td>
</tr>
<tr>
<td>Neurological recovery†</td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td>3.5 (1.8–6.6)</td>
</tr>
<tr>
<td>IHCA</td>
<td>4.2 (1.2–14.9)</td>
</tr>
<tr>
<td>OHCA</td>
<td>2.1 (1.0–4.4)</td>
</tr>
</tbody>
</table>

CPC indicates Cerebral Performance Category; CI, confidence interval; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; and PEA, pulseless electric activity.
*Variables included in multivariable model include age, sex, witnessed arrest, initial rhythm (PEA/asystole), and duration of arrest.
†CPC 1 or 2.
TH in patients with initial nonshockable rhythms, given the lack of randomized controlled trial data, and should encourage its use in this patient population while awaiting data from randomized trials. In addition, if more widespread use of aggressive postarrest care (including TH) in patients with initial nonshockable rhythms is implemented systematically and studied prospectively, further data will be obtained to optimize outcomes in this subpopulation of patients with cardiac arrest, which is increasing in number each year.

Limitations

This study used advanced statistical methodology to limit confounding by indication, and to create 2 study arms, as well, that had similar demographic and arrest characteristics. Despite every effort to minimize bias, we recognize that this methodology does not replace a randomized controlled trial; however, at this juncture, this type of study may be the best means to ethically answer the proposed question.

We used data from the PATH registry; therefore, these outcomes are limited by the retrospective nature of the data, and all other bias frequently encountered from large registry studies, as well. The PATH registry is audited quarterly for trends, with established internal review to ensure the validity of data maintained in the registry.

When conducting our analysis to explore associations between TH and neurological recovery, we accounted for arrest characteristics, and patient demographics, as well. One limitation was that we did not account for inpatient therapy, aside from TH. Specifically, our analysis did not account for the use of early percutaneous coronary intervention, which, in the setting of ventricular dysrhythmia, has been associated with improved outcomes from cardiac arrest.21 Unfortunately, the literature to support percutaneous coronary intervention in nonshockable arrest rhythms is scarce. We do report lack of percutaneous coronary intervention data as a limitation in our analysis; however, given limited data to support this practice, we propose that the use of early percutaneous coronary intervention will undoubtedly be low in our cohort of patients who all had a cardiac arrest with initial nonshockable rhythms.

As is true in most retrospective studies of this nature, patients made “no not resuscitate” or who had “withdrawal of life-sustaining therapy” may alter the outcomes of both patients made “no not resuscitate” or who had “withdrawal of life-sustaining therapy” may alter the outcomes of both

Conclusions

Using propensity score matching to create treatment and control cohorts, we found that patients who experience an arrest with initial nonshockable rhythms (PEA and asystole) have improved neurological outcome when treated with TH versus those who do not receive TH after cardiac arrest. Our findings further support the use of TH in patients with initial nonshockable post–cardiac arrest rhythms, and we encourage further investigation into the utility of neuroprotective strategies in this cohort of patients with cardiac arrest.

Sources of Funding

Dr Perman was supported by an NIH T-32 training grant (5T32 NS061779-05) for the duration of this research project.

Disclosures

Dr Carr spends a portion of his time as the Director of the Emergency Care Coordination Center in the US Department of Health & Human Services. The views expressed here do not necessarily represent the views of the US Government.

References

For over a decade, the utility of therapeutic hypothermia (TH) in patients who have had a cardiac arrest with any underlying nonshockable rhythm (either pulseless electric activity or asystole) has been debated. Undoubtedly, the studies published in 2002 promoted the use of TH in shockable initial rhythms, but did not analyze the benefits for all arrest rhythms. A long-standing request from both the clinical and research communities has been to conduct similar trials of TH in nonshockable initial rhythms; however, many have questioned the ethics behind randomly assigning patients in this type of study. Therefore, we created a cohort of comatose patients resuscitated from cardiac arrest with initial nonshockable rhythms and matched them based on a propensity score. Our analysis is intended to simulate a randomized controlled trial by using this statistical method to account for factors that affected the patients’ likelihood to receive hypothermia. Half of this cohort was treated with TH, whereas the other half received standard postarrest care (excluding TH). We found that patients who were treated with hypothermia were 3.5 times more likely to survive to hospital discharge neurologically intact, in comparison with those not treated with TH. We also found that patients treated with TH had 2.8 times greater likelihood of overall survival to hospital discharge than those not treated with TH. We hope that these findings will further encourage clinicians to use TH in comatose patients who have survived a cardiac arrest with initial nonshockable arrest rhythms such as pulseless electric activity and asystole.

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