Published in final edited form as:

Resuscitation. 2015 March ; 88: 114–119. doi:10.1016/j.resuscitation.2014.10.018.

Shorter time to target temperature is associated with poor neurologic outcome in post-arrest patients treated with targeted temperature management

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Abstract

Introduction—Time to achieve target temperature varies substantially for patients who undergo targeted temperature management (TTM) after cardiac arrest. The association between arrival at target temperature and neurologic outcome is poorly understood. We hypothesized that shorter time from initiation of cooling to target temperature (“induction”) will be associated with worse neurologic outcome, reflecting more profound underlying brain injury and impaired thermoregulatory control.

Methods—This was a multicenter retrospective study analyzing data from the Penn Alliance for Therapeutic Hypothermia (PATH) Registry. We examined the association between time from arrest to return of spontaneous circulation (ROSC) (“downtime”), ROSC to initiation of TTM (“pre-induction”) and “induction” with Cerebral Performance Category (CPC).

Results—A total of 321 patients were analyzed, of whom 30.8% (99/321) had a good neurologic outcome. Downtime for survivors with good outcome was 11 (IQR 6-27) min vs. 21 (IQR 10-36) min ($p=0.002$) for those with poor outcome. Pre-induction did not vary between good and poor outcomes (98 (IQR 36-230) min vs. 114 (IQR 34-260) ($p=ns$)). Induction time in the good outcome cohort was 237 (IQR 142-361) min compared to 180 (IQR 100-276) min ($p=0.004$).

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Patients were categorized by induction time (<120 min, 120-300 min, >300 min). Using multivariable logistic regression adjusted for age, initial rhythm, and downtime, induction time > 300 min was associated with good neurologic outcome when compared to those with an induction time < 120 min.

Conclusion—In this multicenter cohort of post-arrest TTM patients, shorter induction time was associated with poor neurologic outcome.

Keywords

Targeted Temperature Management; Cardiac Arrest; Resuscitation; Prognosis

INTRODUCTION

The implementation targeted temperature management (TTM) has resulted in improved neurologic outcomes and increased survival for patients suffering from post-cardiac arrest syndrome (PCAS).^{1,2} The mechanism for such neurologic protection is thought to be multifactorial, including limitation of post-arrest endothelial dysfunction, decreased free radical production, and blunting of the post-reperfusion inflammatory cascade.³ However, significant variation in patient outcomes when treated with TTM raises fundamental questions with regard to enrollment of patients in TTM protocols, neuroprognostication, and accurate identification of those individuals who will return to their pre-arrest neurologic state versus those who will remain neurologically devastated.

In animal models, reducing time from successful resuscitation to arrival at target temperature has shown improved neurologic outcome,⁴ but evidence to corroborate these findings in human patients is mixed^{5–8}. Early initiation of TTM has been the mainstay of post-arrest treatment to maximize neuroprotection.⁹ In clinical practice, wide variability in the time to initiate TTM exists.^{6–8,10} Despite protocolized management, substantial variability exists in the time from initiation of TTM to arrival at target temperature (“induction time”) (Figure 1). In contrast to animal studies, which are performed in a highly controlled fashion, clinical investigators have observed that precipitous achievement of target temperature may be associated with poor neurologic outcomes,⁸ perhaps illustrating the complex relationship between injury, early neurologic damage, and patient thermoregulatory control post-arrest. Given that target temperature is static, and cooling devices are programmed to rapidly cool patients to a pre-specified target temperature, variability in time to target temperature is theorized to be secondary to the heat generation produced by the post-arrest patient.

Significant variability in pre-induction and induction time has been observed in post arrest patients treated with TTM. The primary objectives of this study were to examine the relationship between the length of the pre-induction and induction phases of TTM and neurologic outcome. We hypothesized that: 1. Individuals with shorter pre-induction times will survive with better neurologic outcomes as measured by Cerebral Performance Category (CPC). 2. Individuals who suffer greater neurologic injury during their cardiac arrest may exhibit loss of thermoregulatory control and lack of heat generation, resulting in shorter induction times and poor neurologic outcome as measured by CPC.

METHODS

Study design and setting

The Penn Alliance for Therapeutic Hypothermia (PATH) Registry was created in 2010 as a national, on-line repository for patient data from multiple centers performing TTM. Data were utilized from two institutions that utilize the same TTM protocol and supply data to PATH: A large urban, level-1 trauma center, and an academic community affiliate. This study was approved by the University of Pennsylvania Institutional Review Board.

Study subjects and TTM protocols

Patients were considered for inclusion if they were: older than 18 years of age; suffered an in-hospital or out-of-hospital non-traumatic cardiac arrest due to any arrest rhythm; had return of spontaneous circulation (ROSC); remained comatose after arrest; and were treated with TTM (with a goal temperature of 33°C). According to protocol, patients were considered for TTM if they were pulseless for less than 60 minutes and had a Glasgow Coma Motor Score (GMS) of less than 6 after ROSC. Patients were not eligible for TTM if they had evidence of intracranial hemorrhage or bleeding as the etiology of arrest or an active “Do Not Resuscitate” (DNR) order. After inclusion in the study, patients were excluded from analysis if they had withdrawal of life sustaining therapy or TTM withdrawn prior to arrival at goal temperature.

After the decision to initiate TTM was made, care administered during the induction phase was performed based on shared protocols at the two institutions. Cooling was initiated with 1-2 liters of chilled normal saline infused through peripheral intravenous cannulae and placement of external fluid filled wraps connected to a thermostatically-controlled cooling unit (MediTherm III, Stryker, Kalamazoo, MI). Patient temperatures were recorded via either an esophageal or bladder catheter probe. TTM was initiated either in the Emergency Department, Cardiac Catheterization Laboratory or Intensive Care Unit. Further details of the TTM protocols employed at these two institutions have been published elsewhere (www.med.upenn.edu/resuscitation/hypothermia/protocols.shtml).¹¹

Data collection

Descriptive data were obtained for each subject, including age at arrest, sex, race, and body mass index (BMI, calculated using measured height and weight at the time of intensive care unit admission). Arrest characteristics, including year, initial rhythm, and “downtime” (time from cardiac arrest to when return of pulse was achieved) were abstracted from the medical record and recorded within the PATH database by trained research assistants at the two participating institutions. Specific time intervals measured include the pre-induction phase and the induction phase (Figure 1). The primary outcome was neurologic status at hospital discharge recorded as CPC, dichotomized into “good” (CPC 1-2) and “poor” (CPC 3-5) outcomes¹²⁻¹⁴. Prior work has demonstrated that discharge CPC correlates well with longer-term outcomes.¹⁵

Statistical analysis

Demographic data and arrest characteristics were examined using summary statistics, and comparisons were made using chi-square and student's t-tests (Table 1). Median downtime, pre-induction time and induction times were compared for patients with a “good” and “poor” neurologic outcome via Mann-Whitney U analysis for non-parametric data (Table 2). Demographic and arrest characteristics were analyzed using univariate logistic analysis to determine association with neurologic outcome. A Kaplan-Meier (KM) plot was created to illustrate the unadjusted induction time for patients with a “good” versus “poor” neurologic outcome, and a log-rank test was utilized to test the hypothesis that the KM curves were different (Figure 2).

Induction time was categorized into three groups by analyzing the cohort as a whole. Patients were divided into the following categories: 1) <120 min, 2) 120 - 300 min and 3) > 300 min. Groups 1 and 3 contain patients with induction time in the respective outlying quartiles, intended to represent extremes in induction time with group 1 cooling more rapidly and group 3 cooling over a longer duration of time. Multivariable logistic regression was employed to assess the association between induction time categories and poor neurologic outcome adjusting for relevant covariates as determined by the previous univariate analysis. Standard statistical software (Stata v. 12.1., Statacorp, College Station, TX) was used to analyze the data. Statistical significance was set at $p < 0.05$.

RESULTS

Population, demographics, arrest characteristics

We identified 342 patients from the PATH database who received TTM after cardiac arrest from 5/2005 to 1/2013. Thirteen patients were then excluded as they had TTM initiated but did not arrive at target temperature secondary to re-arrest, withdrawal of care, or physician decision to discontinue therapy. Two patients were excluded as they arrested secondary to trauma and intracranial hemorrhage. Finally, six patients were excluded as they were transferred from outside hospitals, and had insufficient documentation regarding their initial management. Thus, a final group of 321 patients was included in this study.

Over half of patients (52.7%) analyzed in this study had an out-of-hospital cardiac arrest. Just under a quarter of patients (23.3%) were patients transferred to the two facilities for post-arrest management. The transfer population was similar to the full cohort in age and gender however, these patients had a higher incidence of initial shockable rhythm in comparison to the OHCA/IHCA cohort (43.8% vs. 27.9%, $p = 0.02$).

Demographic and arrest characteristics for patients stratified by neurologic outcome are shown in Table 1. Patients with poor neurologic outcome were older than those with good neurologic outcome (60.2 ± 17.1 vs. 53.1 ± 15.8 , $p = 0.005$), had a lower rate of shockable initial rhythms (23% vs. 60%, $p < 0.001$), and were more often African American (51% vs. 36%, $p = 0.028$). There were no significant differences between the two cohorts with regard to sex or BMI. Initial temperature was evaluated in a subset of patients ($n = 104$). There was no difference in initial temperature recorded after ROSC in patients who ultimately had a “good” vs. “poor” neurologic outcome ($35.6^\circ\text{C} \pm 1.9^\circ\text{C}$ vs. $35.3^\circ\text{C} \pm 1.8^\circ\text{C}$; $p = 0.42$). There

was no association between year of arrest and outcome, indicating that a temporal trend towards survival was unlikely in this cohort (OR 0.96; 95% CI 0.84-1.10, $p=0.55$).

Downtime, Pre-induction, Induction Time

Table 2 displays median downtime, pre-induction time, and induction time stratified by neurologic outcome. Patients with a poor neurologic outcome had significantly longer downtimes versus patients who had good neurologic recovery (21 (IQR 10-36) vs. 11 (IQR 6-27) min, $p=0.002$). There was no statistical difference in pre-induction time between patients with good versus poor outcomes. For patients who recovered with a CPC of 1 or 2, the median induction time was significantly longer than for patients discharged from the hospital with a CPC of 3-5 (180 (IQR 100-276) vs. 237 (IQR 142-361) min, $p=0.004$).

A Kaplan-Meier curve of univariate induction time demonstrates that patients with poor neurologic outcome arrive at target temperature more rapidly than patients with good neurologic outcome ($p<0.001$) (Figure 2.).

Stratifying patients by induction time

Patients with short induction times (<120 minutes) were more likely to have poor neurologic outcomes (32.5% vs. 15.6%; $p=0.003$) (Table 3). Patients with long induction times (>300 minutes) were more likely to have good neurologic outcomes (35.6% vs. 18.9%; $p=0.002$). No statistical difference in neurologic outcomes was observed among patients with induction time between 120 and 300 minutes.

Univariate analysis, adjusted logistic regression

We completed univariate analysis of possible predictor variables to test for association with neurologic outcome (Table 4). Pre-induction time demonstrated no important association with neurologic outcome ($p=0.677$). Induction time (categorized into tertiles) as a predictor variable demonstrated a statistically important association with neurologic outcome (120-300 mins: OR 2.11, 95% CI 1.07-4.14, $p=0.031$; >300 mins: OR 3.93, 95% CI 1.87-8.25, $p<0.01$). We also found that age at time of cardiac arrest, initial shockable rhythm and downtime in minutes were significantly associated with neurologic outcome (Table 4). All variables significantly associated with neurologic outcome were included in the final model.

Our final multivariable logistic model indicated that patients with an induction time >300 minutes have a higher likelihood of survival with good neurologic outcome when compared to those who cooled precipitously (<120 minutes) (OR 2.87, 95% CI 1.26-6.54, $p=0.012$). An induction time between 120 minutes and 300 minutes trended towards an increased survival with good neurologic outcome compared to those who cooled precipitously (<120 minutes) however, this association did not reach statistical significance (OR 1.57, 95% CI 0.74-3.36, $p=0.242$).

DISCUSSION

This study was a multi-center retrospective study investigating the association between pre-induction time, induction time, and neurologic outcome. We found no association between pre-induction time and neurologic outcome. We found that patients who have a prolonged induction time have a greater likelihood of good neurologic outcome, while more precipitous time to target temperature is associated with worse outcomes. In examining this association we determined that age, initial shockable rhythm and duration of downtime were predictor variables associated with neurologic outcome; however, the association between prolonged induction time and improved neurologic outcomes remained intact in adjusted analysis. We interpret this phenomenon as supportive of the theory that patients with more extensive neurologic injury have impaired thermoregulatory control and, therefore, cannot generate heat and “resist” cooling. This is in contrast to those with milder brain injury, possibly recoverable injury, who have more intact thermoregulatory control.

Results of previous reports on time to target temperature or induction time have been varied. Benz-Woerner et al. completed a single center study investigating the association between initial post-ROSC body temperature and the time from hospital admission to arrival at 34° C.¹⁶ The authors found no association between the time variable and neurologic outcome, but did find that patients who had lower post-ROSC body temperatures exhibited worse neurologic outcome. Our study measures induction time as time from initiation of TTM to arrival at goal temperature (33°C), a more accurate depiction of true induction time in comparison to the time used by the authors in the aforementioned study.

Haugk et al. analyzed 588 patients at a single center, measuring time from ROSC to target temperature (< 34°C) using an esophageal temperature probe.⁸ This methodology differed from our study, in that we targeted time from induction of cooling to arrival at target temperature (33°C). The authors divided their cohort into tertiles (<120 mins, 120-220 mins, >220 mins) and found an 86% increase in odds of good neurologic outcome with each advancing tertile. Interestingly, Haugk et al. did not include CPC 5 patients in their analysis, only considering CPC 3 and 4 as their “poor” outcome. Although there are significant dissimilarities in methodology between this work and ours, the trend in prolonged induction time correlating with improved neurologic outcomes remains.

In contrast to our study as well as that of Haugk et al., there has been a group of studies supporting the theory that more rapid induction of TTM is correlated with improved neurologic outcome. Sendelbach et al. found that with every 30 minute delay at reaching target temperature there was a trend towards worse neurologic prognosis, although statistical significance was not obtained.⁶ The cohort examined in this study consisted predominantly of individuals with an initial shockable rhythm (73%). Similarly, Wolff et al. found that shorter time to target temperature was associated with better neurologic outcome⁵, however, this study was conducted using an endovascular cooling device, measured from the time from collapse to target temperature, and 84% of the patients had an initial shockable rhythm. The difference between our results and those reported in this group of articles may be due to the aforementioned methodologic differences. Given the high incidence of shockable initial rhythm, the prior studies may have examined a cohort of patients with a higher incidence of

cardiac disease as the etiology of their arrest. In our total cohort, the incidence of shockable initial rhythm was only 32%.

Despite the variation of results observed in the literature, our findings are consistent with biologic plausibility. The hypothalamus and brainstem are responsible for thermoregulatory control¹⁷ and damage to these areas may be responsible for the phenomenon we observed. This same pathophysiologic response may also describe the findings of Benz-Woerner et al. when they found that patients with poor neurologic outcome had a lower core temperature upon ROSC.¹⁶ Nair et al. found that patients with a good neurologic outcome were more apt to shiver,¹⁸ thus indicating an intact thermoregulatory response to hypothermia. The TTM protocol utilized in this study includes anti-shivering therapy (ie. paralytic/sedative medications) to facilitate rapid reduction in core temperature, which would minimize shivering as heat generation but does not alter other metabolic and physiologic mechanisms for heat generation.

In order to reduce the risk of early or inaccurate prognostication, some investigators have recommended the use of a multimodal approach to predict neurologic outcome.¹⁹ Prognostic tests such as computed tomography (CT) of the brain, continuous electroencephalography (cEEG), neuron-specific enolase (NSE) and somatosensory evoked potentials (SSEP) have yielded valuable information, however, each test in isolation has raised some concern amongst investigators.²⁰ In order to provide neurologic prognosis in an algorithmic approach, we propose that induction time may complement prior neurologic testing and assist clinicians in determining appropriate levels of care early in the course of PCAS, and aid families by providing objective prognostic information.

In addition to aiding in prognostication, if more rapid induction time is indicative of greater neurologic injury, it is possible that these patients may have suffered greater ischemic injury and therefore, may be a population that would benefit from longer duration of maintenance therapy (i.e. 48 or 72 hours of TTM versus the standard 24 hours of TTM). As described by Sawyer et al., a novel ischemic ratio may be predictive of injury and contribute to refining treatment based on injury.²¹ Further investigation into tailoring patient care based on measurements is necessary and may contribute to improved outcomes.

Recently, Nielsen et al. reported no difference in neurologic outcome when patients were randomized to 36° versus 33° C for the maintenance phase of TTM.²² This finding supports the necessity for further investigation into thermoregulatory control post-arrest, as we propose that patients who have been significantly injured, may lack the thermoregulatory control to remain at 36°C thus requiring warming to maintain that core temperature, again, findings that could be concerning for greater neurologic injury.

LIMITATIONS

There are recognized limitations to this study. Primarily, this was a retrospective analysis that was limited by data that could be extracted from chart review. Cardiac arrest literature is plagued by the difficulty of gathering accurate time data, and therefore, we recognize that chart documentation, especially pertaining to downtime, may not have yielded the most

accurate time intervals. We do not report initial temperatures for all patients in this cohort. In review of the data, there was significant variation in when patients had their first temperature recorded post-arrest, with some patients not having a temperature recorded until they had already received cold saline and had TTM initiated. Given this lack of uniformity, we only report a small subset of our cohort. Additionally, we do not report rates of bystander CPR, a recognized limitation in our pre-hospital reporting. Our primary outcome, neurologic outcome at hospital discharge as described by CPC score, does not incorporate long-term recovery, and cardiac arrest patients have been shown to improve upon their CPC after discharge from the hospital. However, investigations have suggested that discharge CPC is largely predictive of long-term outcome. Finally, our intention was to use a cohort of patients who had TTM via similar clinical protocols so as to reduce the variability seen in other registry studies. This resulted in a smaller sample size for our study. Despite our smaller sample size, a significant association between shorter induction time and poor neurologic outcome was observed.

CONCLUSION

We found that patients with shorter induction times suffered worse neurologic outcome versus those with more prolonged induction times. No difference in pre-induction time was found in this cohort of post-arrest patients. Further study is needed to determine if induction time may assist in improving upon neurologic prognostication or treatment algorithms in comatose survivors of cardiac arrest who undergo therapeutic hypothermia.

Acknowledgments

Funding Sources

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

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Figure 1.

The phases of Targeted Temperature Management (TTM) in post cardiac arrest syndrome. A schematic diagram depicting the first 72 hours post return of spontaneous circulation (assuming a starting temperature of normothermia and a maintenance temperature of 33°C).

Figure 2. Kaplan-Meier Curve illustrating induction time for PCAS patients with "good" vs. "poor" neurologic outcome ($p < 0.001$).

Table 1

Patient demographics and arrest characteristics

Characteristics	“Poor” Neurologic Outcome (n=222)	“Good” Neurologic Outcome (n=99)	p-value
Age	60.2 ± 17.1 yrs	53.1 ± 15.8 yrs	0.005
Male	59% (130)	62% (61)	ns
Race			
African American	51% (112)	36% (36)	0.028
Caucasian	39% (86)	49% (48)	ns
Other	8% (18)	10% (10)	ns
BMI	28.9 ± 7.4	30.5 ± 8.0	ns
Shockable initial rhythm (VF/pVT)	23% (49)	60% (52)	<0.001
Location of Arrest			
In-hospital	25% (56)	22% (22)	ns
Out-of-hospital	54% (120)	51% (50)	ns
Transfer	21% (46)	27% (27)	ns

BMI: body mass index; VF: Ventricular fibrillation; pVT: Pulseless ventricular tachycardia

Table 2

Median downtime, pre-Induction time, and induction time for patients with “good” vs. “poor” neurologic outcome

Time interval	“Poor” Neurologic Outcome (n=222)	“Good” Neurologic Outcome (n=99)	p-value
Downtime (n=300)	21 (10-36) mins	11 (6-27) mins	0.002
Pre-induction Time (n=288)	114 (34-260) mins	97.5 (36-230) mins	ns
Induction Time (n=296)	180 (100-276) mins	236.5 (142-361) mins	0.004

Table 3

Proportion of patients with Poor vs. Good neurologic outcome by induction time divided into three categories.
(n=296)

Induction time	range	“Poor” Neurologic Outcome	“Good” Neurologic Outcome	p-value
<120 min	0-120 min	32.5% (67)	15.6% (14)	0.003
120-300 min	122-300 min	48.5% (100)	48.9% (44)	0.96
>300 min	304-1220 min	18.9% (39)	35.6% (32)	0.002

Table 4

Univariate and multivariable analysis^{*} to examine the association between variables listed below and neurologic outcome.

Variable	OR	95% CI	Univariate p-value	Multivariable p-value
Age	0.98	0.962-0.990	0.001	0.001
Sex	0.88	0.542-1.430	0.606	-
Race	1.25	0.850-1.842	0.257	-
BMI	1.03	0.995-1.06	0.097	-
Shockable	4.84	2.85-8.25	0.000	0.000
Location				
In-Hospital	-	-	-	-
Out-of-Hospital	1.08	0.59-1.99	0.80	-
Transfer	1.54	0.77-3.01	0.22	-
Downtime	0.98	0.96-0.99	0.002	0.001
Preinduction Time	0.99	0.99-1.00	0.678	-
Induction Time	1.00	1.001-1.003	0.004	-
Induction Time (Categorized)				
<120 min	-	-	-	-
120-300 min	2.11	1.07-4.04	0.031	0.242
>300 min	3.57	1.77-7.21	<0.001	0.012

The values **bolded** indicate the variables included in the multivariable logistic model addressing the association between induction time in tertiles and neurologic outcome.

^{*} The multivariable model incorporates patients with complete data (n=282)