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Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest☆

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ABSTRACT

Objective: Therapeutic hypothermia, also known as targeted temperature management (TTM), improves clinical outcomes in patients resuscitated from cardiac arrest. Hyperthermia after discontinuation of active temperature management ("rebound pyrexia") has been observed, but its incidence and association with clinical outcomes is poorly described. We hypothesized that rebound pyrexia is common after rewarming in post-arrest patients and is associated with poor neurologic outcomes.
Methods: Retrospective multicenter US clinical registry study of post-cardiac arrest patients treated with TTM at 11 hospitals between 5/2005 and 10/2011. We assessed the incidence of rebound pyrexia (defined as temperature >38 °C) in post-arrest patients treated with TTM and subsequent clinical outcomes of survival to discharge and "good" neurologic outcome at discharge, defined as cerebral performance category (CPC) 1–2.
Results: In this cohort of 236 post-arrest patients treated with TTM, mean age was 58.1 ± 15.7 y and 106/236 (45%) were female. Of patients who survived at least 24 h after TTM discontinuation ($n = 167$), post-rewarming pyrexia occurred in 69/167 (41%), with a median maximum temperature of 38.7 (IQR 38.3–38.9). There were no significant differences between patients experiencing any pyrexia and those without pyrexia regarding either survival to discharge (37/69 (54%) v 51/98 (52%), $p = 0.88$) or good neurologic outcomes (26/37 (70%) v 42/51 (82%), $p = 0.21$). We compared patients with marked pyrexia (greater than the median pyrexia of 38.7 °C) versus those who experienced no pyrexia or milder pyrexia (below the median) and found that survival to discharge was not statistically significant (40% v 56% $p = 0.16$). However, marked pyrexia was associated with a significantly lower proportion of CPC 1–2 survivors (58% v 80% $p = 0.04$).
Conclusions: Rebound pyrexia occurred in 41% of TTM-treated post-arrest patients, and was not associated with lower survival to discharge or worsened neurologic outcomes. However, among patients with pyrexia, higher maximum temperature (>38.7 °C) was associated with worse neurologic outcomes among survivors to hospital discharge.

1. Introduction

Therapeutic hypothermia improves both survival and neurologic outcome when initiated after resuscitation from cardiac arrest.[1–4] Contemporary protocols for therapeutic hypothermia, known more broadly as therapeutic temperature management (TTM), consist of a cooling phase, a maintenance phase in which temperature is held at 32–34 °C, and a rewarming phase in which normothermia is restored and active temperature control is removed. Subsequent to rewarming, "rebound pyrexia" has been observed, with temperature elevations >38 °C within 24 h of the cessation of active temperature control. Pyrexia has been associated with worsened neurologic outcomes in other disease states such as subarachnoid hemorrhage and traumatic brain injury.[5,6] While investigations have evaluated temperature dynamics during induction and maintenance of post-arrest TTM,[7–9] rebound pyrexia

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immediately following post-arrest TTM remains poorly characterized with regard to frequency as well as its association with clinical outcomes.

We sought to measure the incidence of rebound pyrexia in patients who received post-arrest TTM. We hypothesized that post-rewarming pyrexia was common and would be associated with worsened clinical outcomes at hospital discharge following cardiac arrest.

2. Methods

A retrospective analysis was performed using data from the Penn Alliance for Therapeutic Hypothermia (PATH) registry. PATH was established in 2010 as a multicenter U.S.-based registry hosted by the University of Pennsylvania Health System, to serve as a clinical data repository for cardiac arrest and post-arrest care. All PATH member institutions received Institutional Review Board approval or waiver to participate in studies of the pooled registry data. The current investigation received approval from the University of Pennsylvania Institutional Review Board.

2.1. Penn Alliance for Therapeutic Hypothermia (PATH) registry

Each patient record in PATH consists of 30 data elements required for quality assurance purposes from all participating institutions. One hundred additional data elements are required for research participation. Further optional data elements are available to address specific research questions. The full list of elements can be found at the PATH Internet site.[10] Data are entered via a secure Internet portal and maintained on a password-protected encrypted server at our institution. Both out-of-hospital and in-hospital cardiac arrest events are eligible for entry into the PATH registry, with an arrest event defined as the loss of a pulse requiring the documented delivery of chest compressions.

Data were collected retrospectively at each of the participating institutions and entered into PATH by a trained healthcare provider. Before entering data, these clinicians are first trained by the PATH database manager using a structured approach including mock case entry and case review. All participants are provided with a standardized data dictionary for PATH data elements and frequent telephone contact is made with each data abstracter early in registry participation. Additionally, a formal auditing process is conducted on a selection of cases to ensure data integrity, with feedback given to site abstractors for correction. The database manager has access to all entered records from each participating hospital. Currently there are 17 institutions from 11 states participating in the PATH registry project (see Fig. 1).

2.2. Targeted temperature management (TTM)

Post-cardiac arrest TTM can be described in three phases: cooling, maintenance, and rewarming. The cooling phase is defined in the PATH registry as the time interval from when cooling techniques are initiated (e.g., cold saline or external cooling pads) until the goal target of 32–34 °C is reached. The maintenance phase is defined as the time interval from reaching 34 °C until the process of active warming is initiated. In most hospital protocols, this period of time is set at 24 h, with temperature recorded hourly during this phase and during post-arrest care more generally. The rewarming phase then lasts from this moment until achievement of 37 °C ("normothermia"). Pyrexia is defined in the current work as a documented temperature greater than 38 °C up to 24 h after rewarming, consistent with prior investigations.[11,12] Good neurologic outcome is defined as a documented cerebral performance category (CPC) of a 1 or 2 at hospital discharge. CPC was assessed as part of the retrospective medical record review from patient charts after hospital discharge.

2.3. Institutions

Of the 17 institutions participating in PATH, 11 had completed records in the database at the time of analysis, therefore these institutions were included in this study – six additional hospitals only submitted incomplete records at the time of analysis. See Table 1 for hospital demographic information and TTM protocol standards including rewarming protocols and controlled normothermia protocols after rewarming.

Fig. 1. Distribution of 11 states with participating PATH registry institutions.

Table 1
Hospital demographics and targeted temperature management (TTM) protocol information.

Hospital	Type	Bed size	Trauma center	Cath lab (24/7)	OHCA	TTM eligible (annually)	TTM protocol	Rewarming rate	Controlled normothermia, duration
Hospital A	C	300	No	Yes	120	15	Yes	0.5 °C/hr	Yes, 48 hrs
Hospital B	C	265	Yes	Yes	12	7	Yes	0.2–0.3 °C/hr	No
Hospital C	A/T	763	Yes	Yes	150	70	Yes	0.25 °C/hr	No
Hospital D	A/T	424	Yes	Yes	ND	27	Yes	1.0 °C/hr	No
Hospital E	C	400	Yes	Yes	60	23	Yes	ND	No
Hospital F	A/T	309	No	Yes	80	25	Yes	0.7 °C/hr	No
Hospital G	A/T	814	Yes	Yes	101	54	Yes	0.33 °C/hr	No
Hospital H	A/T	900	Yes	Yes	70	65	Yes	0.25 °C/hr	No
Hospital I	A/T	331	No	Yes	68	26	Yes	0.33 °C/hr	No
Hospital J	C	520	No	Yes	45	12	Yes	0.5 °C/hr	No
Hospital K	A/T	719	Yes	Yes	240	25	Yes	0.3 °C/hr	Yes, 48 hrs

The 11 hospitals included in the study are represented by letters to protect their anonymity. Therapeutic Hypothermia eligibility defined by local hospital protocol; OHCA, out of hospital cardiac arrest; IHCA, in-hospital cardiac arrest; C, Community Hospital; A/T, Academic/Teaching hospital; ND, not documented; °C/hr, degree Celsius per hour; hrs, hours.

2.4. Statistical analysis

Descriptive data were exported from the PATH registry into a spreadsheet application (Excel, Microsoft Corp., Redmond, WA) and are presented as means with standard deviations (SD) or medians with interquartile ranges for continuous data and frequencies and percentages for categorical data. To determine differences between pyrexia and non-pyrexia or high pyrexia and no/or low pyrexia, Student's *t*-test was used for continuous data such as age, downtime, time to target temperature; chi-square or Fisher's exact test for categorical data (gender, survival, neurologic outcome) and Wilcoxon rank sum for LOS. All analyses were performed using SAS statistical software (Version 9.3, SAS Institute, Cary, NC). A probability of $p < 0.05$ was considered statistically significant.

3. Results

A total of 2023 adult cardiac arrests from 11 institutions were evaluated for inclusion in the current analysis, occurring between 5/2005 and 10/2011. Of those, 981/2023 (49%) cases exhibited return of spontaneous circulation (ROSC) and 236/981 (24%) were treated with TTM following resuscitation. The 236 TTM-treated patients served as the primary cohort for this investigation.

Demographic and event data from the TTM-treated cohort are shown in Table 2. The mean age was 58.1 ± 15.7 y; 106/236 (45%) were female and 76/236 (32%) had ventricular fibrillation/ventricular tachycardia (VF/VT) as an initial rhythm. Cooling methods for the TTM-treated cohort included chilled intravenous saline 188/236 (80%), ice 47/236 (20%), surface cooling 207/236 (88%) and endovascular cooling 4/236 (2%). Mean cooling duration was 23.5 ± 8.3 h and mean rewarming time was 15.4 ± 12.4 h. Of those who were treated with TTM, 98/236 (42%) survived to discharge with 77/98 (79%) exhibiting good neurologic outcomes.

Of the patients who survived 24 h after post-TTM rewarming, pyrexia occurred in 69/167 (41%) with a median maximum temperature of 38.7 °C (IQR 38.3, 38.9). The highest temperature in any pyrexic patient was 40.8 °C (see Fig. 2). Demographic information, co-morbidities and arrest characteristics were similar between those who experienced pyrexia and those who did not, except that pyrexic patients were younger and had somewhat shorter rewarming durations (see Table 3). Fifty-two percent (36/69) of pyrexic patients were treated for their increased temperature using multiple methods including acetaminophen (69%), ice application to skin (17%), re-application of the cooling device (11%), antibiotics (11%) and other methods (11%). Of those who had pyrexia, all were treated at institutions that did not have controlled normothermia protocols defined as leaving the cooling device in place for a set period of time after rewarming (see Table 1). Median length of stay was similar

Table 2
TTM cohort demographics and clinical data ($n = 236$).

Mean age, y ± SD	58.1 ± 15.7
Gender, *n* (%)	
Female	106 (45%)
Male	130 (55%)
Location, *n* (%)	
Out-of-hospital	187 (79%)
In-hospital	44 (19%)
Not listed	5 (2)%
Initial rhythm, *n* (%)	
VF/VT	76 (32%)
PEA	85 (36%)
Asystole	61 (26%)
Other/unknown	14 (6%)
Time intervals	
Arrest duration, m ± SD	28 ± 23
Time to target temp, h ± SD	4.0 ± 4.2
TTM maintenance duration, h ± SD	23.5 ± 8.3
Rewarming duration, h ± SD	15.5 ± 12.4
Outcomes	
Survival to discharge, *n* (%)	98 (42%)
CPC 1 or 2 (among survivors), *n* (%)	77 (79%)

TTM, targeted temperature management; SD, standard deviation; VF/VT, ventricular fibrillation/ventricular tachycardia; PEA, pulseless electrical activity; CPC, cerebral performance category.

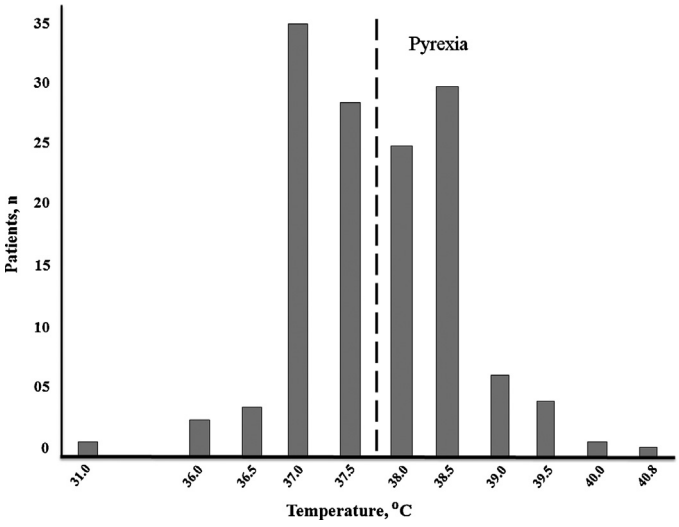

Fig. 2. Frequency histogram of maximum temperatures during the 24 h period following post-arrest TTM rewarming. The dashed line represents the cut-off defining pyrexia in this investigation.

Table 3
Any post-TTM pyrexia cohort versus no pyrexia cohort.

	Pyrexia (n = 69)	No pyrexia (n = 98)	p value
Female, n (%)	21 (30)	43 (44)	0.11
Mean age, y ± SD	53.1 ± 12.9	58.9 ± 15.1	0.002
Comorbidities			
Cardiac disease	40 (58)	60 (61)	0.673
Diabetes mellitus	16 (23)	26 (27)	0.624
Renal insufficiency	5 (7)	12 (12)	0.293
Respiratory disorder	5 (7)	15 (15)	0.114
Seizure disorder	3 (4)	4 (4)	0.660
Septicemia	0 (0)	1 (1)	0.400
Stroke	2 (3)	6 (6)	0.337
VF/VT, n (%)	33 (48)	34 (35)	0.11
Median maximum temperature	38.7 °C	37.2 °C	<0.001
Mean arrest duration, m ± SD	24 ± 22.4	25 ± 21.6	0.76
Mean time to target temperature, h ± SD	3.96 ± 4.8	3.94 ± 4.0	0.97
Duration of TTM maintenance phase, h ± SD	25 ± 8.6	24 ± 5.0	0.44
Duration of rewarming, h ± SD	13 ± 6.9	18 ± 15.6	0.01
Median length of stay, d (IQR)	11 d (5.5, 20.7)	10 d (6.5, 18.2)	0.67
Survival to discharge, n (%)	37 (54)	51 (52)	0.88
Survival with CPC 1–2, n (%)	26 (70)	42 (82)	0.21

TTM, targeted temperature management; SD, standard deviation; VF/VT, ventricular fibrillation/pulseless ventricular tachycardia; IQR, interquartile range; CPC, cerebral performance category.
Cardiac disorders include congestive heart failure, coronary artery disease, myocardial infarction; respiratory disorders include asthma, chronic obstructive pulmonary disease, respiratory insufficiency, and pneumonia.

Table 4
High post-TTM pyrexia cohort compared to mild pyrexia/no pyrexia cohort.

	High pyrexia (n = 30)	Mild/no pyrexia (n = 137)	p value
Female, n (%)	20 (67)	83 (61)	0.38
Mean age, y ± SD	53.0 ± 12.1	57.1 ± 14.9	0.17
VF/VT, n (%)	11 (36)	48 (35)	0.67
Maximum mean temperature	39.2 ± 0.5	37.5 ± 0.9	<0.0001
Mean arrest duration, m ± SD	26 ± 28.8	24.1 ± 19.9	0.70
Mean time to target temperature, h ± SD	4.1 ± 5.0	3.9 ± 4.2	0.84
Duration of TTM maintenance phase, h ± SD	24.6 ± 4.6	24.3 ± 7.2	0.84
Duration of rewarming, h ± SD	13.2 ± 7.5	16.9 ± 13.7	0.17
Median length of stay, d (IQR)	10.0 (7.8, 17.9)	10.9 (5.8, 20.6)	0.71
Survival to discharge, n (%)	12 (40)	76 (56)	0.16
Survival with CPC 1–2, n (%)	7 (58)	61 (80)	0.04

TTM, targeted temperature management; SD, standard deviation; VF/VT, ventricular fibrillation/pulseless ventricular tachycardia; IQR, interquartile range; CPC, cerebral performance category.

between patients with and without pyrexia (11 d (IQR 5.5, 20.7) v 10 d (IQR 6.5, 18.2), p = 0.67). Subjects with pyrexia showed no statistically significant difference in survival to discharge (37/69 (54%) v 51/98 (52%), p = NS) or good neurologic outcome (42/51 (82%) v 26/37 (70%), p = NS) versus those who did not become pyrexic.

In a secondary analysis, we further evaluated the subgroup of post-arrest patients with marked pyrexia (patients above the median pyrexia temperature of 38.7 °C) compared to the remainder of the post-arrest TTM cohort (see Table 4). Demographic and arrest characteristics were similar between the two subgroups in this comparison. No statistically significant differences in survival to discharge were found between the two groups (40% v 56% p = 0.158). However, the subgroup with marked pyrexia had a significantly smaller proportion of CPC 1–2 survivors at hospital discharge compared to the remainder of the TTM cohort with either mild or no pyrexia (58% v 80% p = 0.04). Time of onset between those with marked pyrexia compared to those with mild pyrexia was indistinguishable when grouped into onset at 0–24 h, 25–48 h and greater than 48 h (data not shown).

4. Discussion

In this multicenter analysis of resuscitated cardiac arrest patients treated with TTM, pyrexia within 24 h after rewarming was frequent (occurring in 41% of patients) and pronounced (pyrexic patients had a median temperature maximum of 38.7 °C). Patients with any magnitude of pyrexia had similar survival to discharge and neurologic status at discharge to patients without temperature elevations. However, pyrexia with temperature greater than the median temperature of 38.7 °C was associated with worse neurologic status but not overall survival at discharge.

Little is known about the frequency of post-arrest pyrexia from prior studies of TTM-treated patients. One prior single center investigation that described a set of post-arrest adverse effects in a 69 patient group found that post-rewarming pyrexia, which was defined in as >38 °C beginning at cooling through five days post-rewarming, occurred in 17% of their cohort.[11] Another single center study, examining differences between external and intravascular cooling devices after cardiac arrest, found the rate of post-TTM pyrexia (again defined as >38 °C) was similar in both groups, occurring in approximately 60% of patients.[12] A recent study examining rewarming rates in post-cardiac arrest TTM patients also found that a fever greater than 38 °C within the first three days after ROSC was not associated with outcome, although their study did not distinguish between mild pyrexia and pronounced pyrexia.[13] Our work, with a larger multicenter cohort, found an intermediate frequency of post-TTM pyrexia compared to these three studies. Differences in pyrexia rates may depend on TTM protocol variations, such as rewarming rates, and local variations in practice regarding fever treatment, such as use of antipyretic medications and/or cooling blankets. As shown in Table 1, each participating institution had variable rewarming rates and very few institutions had a controlled

normothermia protocol involving continued use of the TTM device. Comparison of cardiac arrest studies has been made more uniform by the implementation of standardized data elements known as the "Utstein Style" template,[14,15] however no such guidelines exist for reporting post-arrest TTM studies. Development of standardized post-arrest and TTM data elements with consensus definitions would enhance future scholarship surrounding critical care of the resuscitated cardiac arrest patient.

Pyrexia has been studied in the context of other brain injury etiologies and has been associated with poor neurologic outcomes.[16–21] Greer et al. performed a meta-analysis of 39 studies examining the impact of pyrexia on patients suffering from neurologic injuries such as ischemic stroke, hemorrhagic stroke and traumatic brain injury. They concluded that elevated temperature was associated with longer hospital and critical care length of stay, worse functional outcomes and greater mortality rates.[16] In two clinical studies of subarachnoid hemorrhage, pyrexia was associated with worse survival outcomes.[17,18] These studies, and a related group of laboratory investigations,[19–21] demonstrate consistency across acute neurologic disease states in relation to the effect of increased temperature on the brain and its association with adverse clinical consequences. Though our results did not show a statistical difference in neurologic outcomes between the cohorts who experienced any pyrexia versus those who did not experience pyrexia, there was a statistically significant difference between those who had a higher magnitude of pyrexia versus those with a lower magnitude of pyrexia or no pyrexia. This finding is consistent with laboratory studies that also demonstrate a relationship between magnitude of pyrexia and extent of neurologic injury.[21] Taken together, these findings suggest that the effect size of post-TTM pyrexia on clinical outcomes is likely modest when pyrexia is of a limited magnitude and/or duration.

Refinements in post-arrest care and TTM protocols are current topics of research interest, including issues of cooling eligibility, cooling rate,[22] adequacy of temperature control during the maintenance phase,[9] and the utility of TTM care regionalization.[23] Among a variety of such refinements, post-TTM pyrexia may represent a readily modifiable problem in real-world TTM implementation, warranting further study. If the association of post-TTM pyrexia with neurologic impairment is confirmed, it is possible that a period of controlled "therapeutic normothermia" following rewarming, using the same TTM techniques, could be tested as an adjunctive approach to post-arrest care. It is interesting to note that only 24% of post-arrest patients in our multicenter cohort received TTM care; the current patient cohort includes patients with non-ventricular fibrillation arrest, and some of our participating hospitals only offer TTM for patients with shockable rhythms; this underscores the issue of eligibility variability in TTM implementation.

The current work has a number of limitations. While representing a multicenter effort based in the US, the size of our patient cohort is relatively small compared to other post-arrest registry investigations from Europe.[24] It is possible that our negative findings with regard to the association of any pyrexia and clinical outcomes are due to insufficient power. In addition, as a retrospective investigation, our work can only test for association and not causation. It is possible that treating or preventing pyrexia would not have an effect on neurologic outcomes, if pyrexia merely represents an "epiphenomenon" of other underlying physiologic derangements that are more direct determinants of clinical outcomes. However, the large body of literature supporting the dangers of pyrexia on neurologic function in brain injury support the face validity of concerns regarding post-arrest pyrexia. As this is a retrospective analysis, data on organ dysfunction and other possible causes for pyrexia were not reliably captured. Finally, as this was a retrospective study, the presumed etiology of pyrexia was generally not documented and therefore not available for review; while believed to be generally due to reperfusion injury phenomena,[25] pyrexia in some patients may reflect new systemic infectious processes following arrest that require other treatment approaches in addition to temperature control.

5. Conclusions

Pyrexia, defined as a temperature $\geq$38 °C within 24 h following rewarming from post-arrest TTM, occurred in 41% of patients in our multicenter cohort. The subset of patients with maximum temperatures above the median pyrexia temperature had worse neurologic status at discharge than patients with milder or no pyrexia. The addition of a period of "therapeutic normothermia" subsequent to TTM rewarming should be evaluated as a component of post-arrest critical care; the duration of this period of time would require further investigation.

Conflict of interest statement

Ms. Leary has received consulting fees from Stryker Medical; Dr. Abella has received honoraria from Medivance Corporation, Stryker Medical and Philips Healthcare and research support from Philips Healthcare; Dr. Gaieski has received honoraria and research support from Stryker Medical.

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Appendix A.

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