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Magnitude of temperature elevation is associated with neurologic and survival outcomes in resuscitated cardiac arrest patients with postrewarming pyrexia☆,☆☆

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ABSTRACT

Purpose: Avoidance of pyrexia is recommended in resuscitation guidelines, including after treatment with targeted temperature management (TTM). Which aspects of postresuscitation pyrexia are harmful and modifiable have not been conclusively determined.
Materials and methods: This retrospective multicenter registry study collected serial temperatures during 72 hours postrewarming to assess the relationship between 3 aspects of pyrexia (maximum temperature, pyrexia duration, timing of first pyrexia) and neurologic outcome (primary) and survival (secondary) at hospital discharge. Adult TTM-treated patients from 13 US hospitals between 2005 and 2015 were included.
Results: One hundred seventy-nine of 465 patients had at least 1 temperature greater than or equal to 38°C. Pyrexic temperatures were associated with better survival than nonpyrexic temperatures (adjusted odds ratio [aOR], 1.54; 95% confidence interval [CI], 1.00-2.35). Higher maximum temperature was associated with worse outcome (neurologic aOR, 0.30 [95% CI, 0.10-0.84]; survival aOR, 0.25 [95% CI, 0.10-0.59]) in pyrexic patients. There was no significant relationship between pyrexia duration and outcomes unless duration was calculated as hours greater than or equal to 38.8°C, when longer duration was associated with worse outcomes (neurologic aOR, 0.86 [95% CI, 0.75-1.00]; survival aOR, 0.82 [95% CI, 0.72-0.93]).
Conclusions: In postarrest TTM-treated patients, pyrexia was associated with increased survival. Patients experiencing postrewarming pyrexia had worse outcomes at higher temperatures. Longer pyrexia duration was associated with worse outcomes at higher temperatures.

1. Introduction

Significant morbidity and long-term impairments are common in cardiac arrest survivors [1-5]. Approximately half of survivors suffer some degree of neurologic disability [3], resulting from ischemic injury occurring during no- and low-flow states as well as reperfusion injury occurring after restoration of native circulation. Collectively, this injury pattern is known as postcardiac arrest syndrome (PCAS) [6,7]. The adverse consequences of PCAS are frequent but variable, ranging from memory loss and proprioceptive derangements to persistent vegetative state [3,4]. Laboratory and clinical studies have suggested that elevated temperatures may exacerbate PCAS and subsequent neurologic injury [8-11].

Two randomized trials from 2002 demonstrated that postarrest therapeutic hypothermia, also known as targeted temperature

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management (TTM), improves neurologic outcomes and survival. In these investigations, patients with out-of-hospital cardiac arrest (OHCA) with initial shockable rhythms were randomized to prompt cooling to 32°C to 34°C for 12 to 24 hours or to passive temperature management [12,13]. Observational studies have confirmed and extended these findings to other cardiac arrest patients [14-21]. However, partially due to concerns that control groups in both trials trended toward elevated mean temperatures and a significant percentage of control patients had pyrexia, a recent multicenter clinical trial [22] randomized both arms to active TTM, 33°C or 36°C. That study found no significant difference in terms of neurologic outcome or mortality, raising the question of whether reduced temperature is the protective component of TTM treatment or if it is avoidance of elevated temperatures [22,23] that is the driver of improved outcomes.

Development of markedly elevated temperatures (pyrexia), often a response to cellular injury, activation of inflammatory cascades, or infection [24], is frequent after cardiac arrest [9,10,25-32]. Markedly elevated temperatures are often a marker of poor outcomes and continued physiologic damage [33-36]; however, whether this is true in postarrest patients, particularly those treated with TTM, has yet to be clearly demonstrated. A connection between pyrexia and worse outcomes in TTM-treated patients has received support in smaller retrospective studies [9-11,37,38], extending findings from earlier research done before the adoption of TTM as standard of care for treatment of anoxic encephalopathy [25,29,39].

We hypothesized that TTM-treated patients with higher maximum temperatures after rewarming will have worse outcomes than those with lower temperatures. We also hypothesized that patients with a longer duration of time at pyrexic temperatures and with earlier onset of pyrexia will have worse outcomes than those with shorter duration and later onset.

2. Materials and methods

To evaluate how body temperature relates to outcomes after reestablishment of post-TTM normothermia, the Penn Alliance for Therapeutic Hypothermia (PATH) registry was queried. Penn Alliance for Therapeutic Hypothermia is an Internet-based registry at the University of Pennsylvania that includes cardiac arrest data from prehospital, emergency department, and in-hospital settings, focusing on postarrest care. Potentially available to any US hospital, it supports tracking patients who experience cardiac arrest and receive cardiopulmonary resuscitation. Data are entered via secure Web site and maintained on a password-protected encrypted server [11]. This project was approved by University of Pennsylvania Institutional Review Board with a waiver of consent.

Serial temperatures in 72 hours after reestablishment of *post-TTM normothermia* (defined as reaching ≥36.5°C [38] after a period of TTM treatment at temperature ≤34.0°C) were evaluated. Patients receiving TTM were included. Exclusion criteria were the following: age 18 years or younger; traumatic etiology of arrest; death in first 24 hours postarrest; and no recorded temperatures during applicable period. Patients also were excluded if target temperature (≤34°C) was never achieved or if they did not survive until completion of rewarming. Out-of-hospital and in-hospital cardiac arrests (IHCA) were included. Most of patients (64%) had temperatures measured via urinary catheters. Seventeen percent had temperature measured via esophageal probes, 8% had it measured rectally, and the rest were measured via other locations.

Pyrexia was defined as greater than or equal to 38.0°C, used in other postarrest studies on effects of temperature [9-11,28,37,38,40]. Primary outcome was neurologic status (measured as Cerebral Performance Category [CPC] score dichotomized into "favorable" [CPC 1-2] and "unfavorable" [CPC 3-5]); secondary outcome was survival, both measured at hospital discharge. There were 3 predefined exposures: maximum temperature, pyrexia duration, and timing of onset of first pyrexic temperature; maximum temperature was the primary exposure of interest.

2.1. Maximum temperature

Maximum temperature was defined as the highest recorded temperature in the 72 hours after completion of TTM and rewarming. Multiple classification approaches were used to account for possibilities of how maximum temperature related to outcomes: as a continuous variable, as an ordinal variable (by single temperature degree), in tertiles, and as a dichotomous variable (≥38.0°C; yes/no) in separate models. Of note, 118 (25%) of patients evaluated for maximum temperature were included in previous work analyzing temperature elevation [11]; the patients in that study were followed up for 48 hours instead of 72 hours and *normothermia* was defined as 37.0°C instead of 36.5°C. In that study, pyrexia duration and timing of onset were not analyzed, so patients were shared only when maximum temperature was analyzed.

2.2. Duration of pyrexia

The duration of time a patient experienced at or above a certain temperature was calculated by adding all time between pyrexic temperature and half of the time between a pyrexic temperature and a nonpyrexic temperature (and vice versa). This calculation ended 72 hours postrewarming and was repeated for every tenth of a degree, beginning with 38.0°C and ending with 42.2°C (highest recorded temperature), to calculate the duration of time at or above each tenth of a degree. This was to assess whether duration of time at different temperatures (eg, 38.0°C, 38.1°C, 38.2°C...42.2°C) had varying relationships to outcomes. Because of diversity in maximum temperature cutoffs across studies [9,11], we analyzed each tenth of a degree to allow for data-driven temperature thresholds. Each measure of time was treated as a continuous variable (hours at temperature of interest) and as an ordinal variable (by tertile) for each temperature cut point.

2.3. Timing of onset of pyrexia

Timing of onset of pyrexia was defined as time between return to normothermia and first recorded pyrexic temperature (≥38°C). Timing of onset of pyrexia was assessed using the following 4 distinct approaches: (1) "early" (first 36 hours postnormothermia) vs (2) "late" (second 36 hours postnormothermia) onset, (3) continuously (hours from normothermia to first temperature, ≥38°C), in deciles, and (4) continuously in groups determined by Jenks natural break optimization, a statistical technique that uses the distribution of data to determine naturally occurring groupings [41,42].

2.4. Patient types

To combine all 3 elements of temperature, 12 different patient categories were created based on naturally occurring groupings, as determined by Jenks natural break optimization [41,42], using 2 groups of maximum temperature (low vs high), 2 groups of pyrexia duration (short vs long), and 3 groups of timing of pyrexia onset (early vs middle vs late; Supplemental Table 1). Patient types were analyzed in univariate with regard to outcomes. Because of some types having a low n, 16 patient types were created involving just 2 dimensions of temperature and analyses repeated.

2.5. Other data analysis

For each dimension of temperature analysis, pre-, intra-, and postarrest variables (Supplemental Table 2) were examined to explore potential confounders. Descriptive statistics used proportions, means and SDs, medians and interquartile ranges, and histograms to determine the proportion or prevalence and distribution of each variable. Each potential