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Fever After Rewarming: Incidence of Pyrexia in Post-Cardiac Arrest Patients who have Undergone Mild Therapeutic Hypothermia

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Abstract

Background—Induction of mild therapeutic hypothermia, or TH (temperature 32–34°C), has become standard of care in many hospitals for comatose survivors of cardiac arrest. Pyrexia, or fever, is known to be detrimental in patients with neurologic injuries such as stroke or trauma. The incidence of pyrexia in the post-rewarming phase of TH is unknown. We attempted to determine the incidence of fever after TH, and hypothesized that those patients who were febrile after rewarming would have worse clinical outcomes than those who maintained normothermia in the post-rewarming period.

Methods—Retrospective data analysis of survivors of out-of-hospital cardiac arrest (OHCA) over a period of 29 months (12/2007–4/2010). Inclusion criteria: OHCA, age > 18, return of spontaneous circulation (ROSC), and treatment with TH. Exclusion criteria: traumatic arrest, pregnancy. Data collected included age, sex, neurologic outcome, mortality, and whether the patient developed a fever (temperature > 100.4°F, 38°C) within 24 hours after being fully rewarmed to a normal core body temperature after TH. We used simple descriptive statistics and Fisher's exact test to report our findings.

Results—A total of 149 patients were identified; of these, 82 (55%) underwent TH. The mean age of the TH cohort was 66 years, and 28 (31%) were female. 54 patients survived for > 24 hours after rewarming and were included in the analysis. Among the analyzed cohort, 28/54 (52%) developed fever within 24 hours after being rewarmed. Outcome measures included in-hospital mortality, as well as neurologic outcome as defined by a dichotomized Cerebral Performance

Category (CPC) score.^{1, 2} When comparing neurologic outcomes between the groups, 16/28 (57%) in the post-rewarming fever group had a poor outcome (CPC score 3–5), while 15/26 (58%) in the no-fever group had a favorable outcome ($P=0.62$). In the fever group, 15/28 (52%) died, while in the no-fever group, 14/26 (54%) died ($P=0.62$).

Conclusion—Among a cohort of patients who underwent mild therapeutic hypothermia after OHCA, more than half of these patients developed pyrexia in the first 24 hours after rewarming. While there were no significant differences in outcomes between febrile and non-febrile patients identified in this study, these findings should be further evaluated in a larger cohort. Future investigations may be needed to determine if post-rewarming temperature management will improve outcomes in this population.

Keywords

Cardiac arrest; fever; therapeutic hypothermia

Introduction

Cardiac arrest (CA) occurs in nearly 350,000 patients in the United States each year with an estimated mortality of 60% in those surviving the initial arrest.³ Moreover, the overall prognosis for survivors is often limited by neurologic injury.^{4, 5} Induction of mild therapeutic hypothermia, or TH (temperature 32–34°C), has become standard of care in many hospitals for comatose survivors of cardiac arrest. Previous studies have demonstrated improved outcomes in patients who suffered out of hospital ventricular fibrillation or ventricular tachycardia cardiac arrest and were treated with TH.^{1, 2}

Pyrexia, or fever, is thought to exacerbate neurologic injury⁶ and is known to be detrimental in the immediate post-arrest period^{7–9} as well as in several other disease states such as stroke^{10, 11} or trauma.^{12, 13} Previous studies examining the role of fever post-cardiac arrest were conducted in the era before mild induced hypothermia became a clinical treatment for these patients. It remains unknown if post arrest patients who develop a fever *following* treatment with therapeutic hypothermia will follow this same trend of increased mortality and morbidity. We hypothesized that fever occurs frequently during the period after induced hypothermia, and that those patients would have poorer outcomes when compared to patients who did not experience fever after rewarming. We further hypothesized that patients who developed a fever while still comatose would have a worse outcome than those comatose patients who did not develop a fever after rewarming; such a finding could suggest that there was ongoing vulnerability for neurologic injury during the comatose period perhaps affected by the phenomenon of hyperthermia. To test these hypotheses, we performed a secondary analysis of data collected in a prospective, observational study of post cardiac arrest patients.

Methods

We performed a retrospective data analysis of survivors of out-of-hospital cardiac arrest (OHCA) over a period of 28 months (12/2007–4/2010) from two tertiary care centers where treatment with therapeutic hypothermia after cardiac arrest became standard of care over the

period from which the data were collected. Approval of each center's Institutional Review Board was obtained. All patients who presented with OHCA were screened for enrollment. Patients were screened by trained research assistants via the hospital's electronic medical record system. Inclusion criteria for the study consisted of adult patients (age ≥ 18 years) who had experienced an OHCA with subsequent return of spontaneous circulation (ROSC) and were comatose at the time of enrollment. Exclusion criteria consisted of pregnant patients, and those with a traumatic etiology of the cardiac arrest.

Pertinent patient demographics including age, sex, race, past medical history, and events leading up to the arrest were recorded at the time of enrollment. All data were collected in the Utstein style.¹⁴ Specific data regarding the arrest event included the location of the arrest, total downtime (total amount of time without a pulse), whether or not the arrest was witnessed, and intra-arrest interventions performed. Vital signs and laboratory data, including complete blood count, electrolytes, arterial blood gas measurements and lactate were recorded at the time of enrollment. Data regarding therapeutic hypothermia were collected, including time of initiation, type of device used, and duration of cooling. It was at the discretion of the treating clinicians whether a patient underwent induced hypothermia. Temperature measurements at serial time points up to one week following ROSC were collected; specifically, it was noted whether the patient developed a fever (defined as a temperature > 100.4°F or 38°C) within 24 hours after being fully rewarmed to a normal core body temperature (37°C) after treatment with mild therapeutic hypothermia (32–34°C). We used simple descriptive statistics and Fisher's exact test to report our findings. Outcome measures included in-hospital mortality, as well as neurologic outcome as defined by a dichotomized Cerebral Performance Category (CPC) score (Figure 1).^{1, 2}

Results

Between the two centers, a total of 149 OHCA patients were identified; of these, 82 (55%) underwent TH. Patients who expired less than 12 hours after the completion of therapeutic hypothermia were not included in analysis, leaving 54 patients (32 from Site 1 and 22 from Site 2) available for analysis (Figure 2). Table 1 describes the baseline characteristics of the cohort included in the study. The mean age of the TH cohort was 66 ± 17 years, and 31% were female. Among the analyzed cohort, 28/54 (52 %) developed fever within 24 hours after being rewarmed to a normal temperature. When comparing neurologic outcomes between the two groups, 16/28 (57%) in the post-rewarming fever group had a poor outcome (CPC score 3–5), while 15/26 (58%) in the no-fever group had a poor outcome (P=0.62). In the fever group, 15/28 (54%) died, while in the no-fever group, 14/26 (54%) died (P=0.62) (Table 2).

Data from one center only (Site 1) included information regarding *neurologic status at the time of the fever*, as well as information about possible sources of infection, and this was considered for a sub-group analysis. Among this particular group, there were 19 patients who were comatose at 24 hours after rewarming, 12 of whom developed a fever post-TH, while seven of these comatose patients did not develop a fever. Among the 12 who developed a fever while comatose, 11 (92%) had a poor neurologic outcome; one patient had a good outcome. All of the comatose patients who did not develop a fever within 24 hours of

rewarming had poor outcomes. When comparing this subgroup of febrile and non-febrile comatose patients within the first 24 hours after rewarming, there was no significant difference in neurologic outcomes between the two groups ($P=1.0$).

Among the cohort from Site 1 who had a fever within 24 hours after rewarming, 8/19 (42%) had positive cultures (blood, urine or sputum) and 14/19 (74%) had a suspicion of infection documented in the discharge summary (most often a pneumonia). Among those patients who did not develop a fever after rewarming, 6/13 (46%) had positive cultures (blood, urine or sputum) and 8/13 (62%) had a suspected infection documented in the discharge summary ($P > 0.05$ for both comparisons). Data about neurologic status at the time of the fever, or infectious complications, were unavailable for the Site 2 cohort.

Discussion

In this post-cardiac arrest cohort treated with therapeutic hypothermia, just over half of these patients developed a fever within 24 hours after rewarming to a normal body temperature. There did not appear to be a significant difference in outcome between those who did and did not develop fever after rewarming. In a subgroup of patients for whom the neurologic status of the patient at the time of the fever was known (comatose vs non-comatose), 92% of patients who developed a fever while still comatose had a poor outcome, and 100% of patients who were comatose at 24 hours but did not develop a fever had a poor outcome. These data do not seem to support the hypothesis that fever after rewarming is harmful, although these findings must be interpreted with caution in such a small sample size. It is unclear whether pyrexia occurring after rewarming simply reflects more profound neurologic injury related to the original cardiac arrest and anoxic brain injury or whether it is secondary to other causes such as infectious complications like pneumonia or bacteremia. Among the subset of patients for whom data about possible infection were available, there was no significant difference in the incidence of culture-confirmed or suspected infection between the fever and no-fever groups. It is important to note that these findings are limited by the lack of available data from the second enrollment site.

There have been previous investigations into elevated temperature after cardiac arrest, although these studies were performed in the era before the routine application of the therapeutic intervention of mild induced hypothermia. Zeiner and colleagues evaluated post-arrest patients between 1992 and 1995 and demonstrated that fever within 48 hours of the arrest was a strong independent predictor for an unfavorable outcome (defined as a CPC score of 3–5), with an odds ratio of 2.26 ($P=0.008$). In this cohort, patients were not treated with TH, and in fact no methods to control temperature were utilized.¹⁵ Takasu and colleagues, in a retrospective study of 43 patients with ROSC after non-traumatic OHCA who were then divided into two groups (clinical brain death and non-clinical brain death), found that there was a significantly higher peak temperature in the clinical brain death group ($P<0.0001$). A peak body temperature greater than 39°C was associated with a higher incidence of clinical brain death, with an odds ratio of 37.8.⁹ These studies, while raising an interesting potential correlation between hyperthermia and worse outcome after cardiac arrest, reflect experience from before the widespread use of therapeutic hypothermia for the care of post-arrest patients; it also does not help to clarify whether fever after arrest is a

cause of poor outcome or simply a result of devastating neurologic injury which has already occurred.

Previous investigations in other disease states where neurologic injury occurs, such as stroke or traumatic brain injury, have demonstrated that fever in the post-injury period is detrimental, leading to poorer clinical outcomes.^{10–13, 16} Mechanisms by which hyperthermia may cause or exacerbate underlying neurologic injury have been explored in animal and human studies and included: increasing cerebral oxygen consumption in areas of the brain which are already ischemic, increasing cerebral blood flow resulting in elevation in intracranial pressure, acceleration of neuronal necrosis, increased free radical production, disturbance of calcium homeostasis, increased vascular permeability and effects on blood-brain barrier permeability.^{17–22} Clinicians who care for post cardiac arrest patients have often extrapolated these data to the neurologically-injured patient who has suffered an ischemia-reperfusion injury as a result of cardiopulmonary arrest. However, there may be differences in the underlying pathophysiology between these diseases which may limit the applicability of these findings to post-arrest patients.

In our study, we included patients with all initial cardiac rhythms: ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, and asystole. There may be differences between these subgroups although it is likely that the final common pathway of cerebral anoxia as a result of cardiopulmonary arrest is the same regardless of initial rhythm; however this remains speculative.

There are several limitations to our study which must be acknowledged. First, this was a retrospective study with the known limitations of such a study design. Data about neurologic status at the time of fever, as well as infectious complications, were not available for one center, further limiting the analysis. Second, our numbers are small, and perhaps have limited us in identifying associations between fever and neurologic outcomes in this population. Future study will need to explore this concept. Third, patients who were not treated with TH were excluded from analysis, and therefore we are unable to state whether those patients who were not treated with TH developed fever in the post-arrest period or had worse clinical outcomes compared with those patients who did receive TH. A large proportion of patients were not treated with TH which likely reflects the time period in which TH became a more commonly accepted clinical intervention and ultimately a standard of care in our institution.

Despite these limitations, our data raise an interesting concern that fever may be common after post-therapeutic hypothermia rewarming. Ongoing temperature management may be an important target for additional intervention after the rewarming process is complete, in order to maximize the benefit of therapeutic hypothermia and other neuroprotective strategies in this population.

Conclusion

In a cohort of out of hospital cardiac arrest patients who underwent therapeutic hypothermia for neuroprotection, more than half of these patients developed a fever in the immediate

post-rewarming period. While there were no significant differences in outcomes between febrile and non-febrile patients identified in this study, these findings should be further evaluated in a larger cohort. Future investigations may be needed to determine if post-rewarming temperature management will improve outcomes in this population; a prospective randomized controlled trial may be warranted.

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Cerebral Performance Category (CPC) Scale	
CPC 1	Good cerebral performance: conscious, alert, able to work
CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life.
CPC 3	Severe cerebral disability: conscious, dependent on others for daily support
CPC 4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. U
CPC 5	Brain death: apnea, areflexia, EEG silence, etc.

Figure 1.
Cerebral Performance Category Definitions

Figure 2.
Study schema

Table 1

Enrolled patient characteristics, overall cohort

Characteristic	
Total number (N)	54
Age – yr. (+/- SD)	66 (17)
Female – no. (%)	16 (31)
Initial arrest rhythm – no. (%)	
Ventricular fibrillation/tachycardia	31 (57)
Pulseless Electrical Activity/Asystole	23 (43)
Downtime (+/- SD)	22 (17.7)
Therapeutic hypothermia (%)	54 (100)
In-Hospital Mortality (%)	29 (54)
Mean CPC (+/- SD)	3.37 (1.86)

Table 2

Enrolled patient characteristics, divided by fever and no-fever within 24 hours after rewarming

Characteristic	Fever	No Fever
Total number (N)	28	26
Age – yr. (+/- SD)	65 (18.5)	68 (17.4)
Female – no. (%)	9 (32)	7 (27)
Initial arrest rhythm – no. (%)		
Ventricular fibrillation/tachycardia	17 (61)	14 (54)
Pulseless Electrical Activity/Asystole	11 (39)	12 (46)
Downtime (+/- SD)	21.3 (16.2)	23.6 (19.5)
Therapeutic hypothermia (%)	28 (100)	26 (100)
In-Hospital Mortality (%)	15 (54)	14 (54)
Mean CPC (+/- SD)	3.36 (1.89)	3.38 (1.88)