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Clinical paper

Body temperature changes are associated with outcomes following in-hospital cardiac arrest and return of spontaneous circulation☆

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ABSTRACT

Introduction: Spontaneous changes in body temperature after return of circulation (ROSC) from cardiac arrest are common, but the association of these changes with outcomes in hospitalized patients who survive to 24 h post-ROSC is not known. We tested the hypothesis that adults who experience temperature lability in the first 24 h have worse outcomes compared with those who maintain normothermia.

Materials and methods: A prospective observational study from a multicenter registry of cardiac arrests (National Registry of Cardiopulmonary Resuscitation) from 355 US and Canadian hospitals. 14,729 adults with return of circulation from a pulseless cardiac arrest. We excluded those who died or were discharged before 24 h post-event, those made Do-Not-Resuscitate (DNR) within 24 h of event, those that had a preceding trauma, and those with multiple cardiac arrests. Finally, we included only subjects that had both a lowest (T_{min}) and highest (T_{max}) body temperature value recorded during the first 24-h after ROSC, resulting in a study sample of 3426 patients.

Results: After adjustment for potential covariates, there was a lower odds of survival in those having an episode of hypothermia (adjusted odds ratio [OR], 0.62; 95% confidence interval [CI], 0.48–0.80), those having an episode of hyperthermia (OR, 0.67; 95% CI, 0.48–0.80), and those having an episode of both (OR, 0.59; 95% CI, 0.39–0.91). Among those who survived to discharge, there was also a lower odds of favorable neurologic performance in those who had an episode of hyperthermia (OR, 0.71; 95% CI, 0.51–0.98).

Conclusions: Episodes of temperature lability following in-hospital resuscitation from cardiac arrest are associated with lower odds of surviving to discharge. Hyperthermia is also associated with fewer patients leaving the hospital with favorable neurologic performance. Further studies should identify whether therapeutic control over changes in body temperature after in-hospital cardiac arrest improves outcomes.

1. Introduction

Most patients that achieve a return of spontaneous circulation (ROSC) after cardiac arrest experience a complex pathophysiologic state with high mortality.[1–4] Neurologic injury, a dominant feature of this post-resuscitation syndrome, occurs during the initial ischemic cascade as well as the reperfusion phase.[5] Post-resuscitation care, particularly through active avoidance of fever and assisted hypothermia, has the potential to improve morbidity and mortality resulting from neurologic injury.[6,7]

There is abundant evidence that hyperthermia exacerbates neuronal injury and hypothermia is neuroprotective in focal and global ischemia models.[8,9] Several clinical studies have even reported an association between elevated body temperature and worse outcomes following resuscitation from out-of-hospital cardiac arrest.[10–12] The eitiology and characteristics of in-hospital cardiac arrests, however, may differ significantly from those occuring out-of-hospital.[13] As well, lack of consistent data collection and significant variation in post-arrest care occuring between institutions could limit external validity.[14,15] With the development of the National Registry of Cardiopulmonary Resuscitation (NRCPR), the AHA has created a robust database of in-hospital cardiac arrests and resuscitation that allows an analysis of body temperature changes as they relate to outcome measures.

In our analysis of adults who achieved ROSC after cardiac arrest and survived to 24-h, we characterized and compared the outcomes of those who had an episode of hyperthermia or hypothermia or

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both with those who maintained normothermia in the first 24-h. We hypothesized that those who experienced temperature elevation would experience worse outcomes when compared to those who maintained normothermia.

2. Methods

2.1. Design and data collection

The NRCPR is a prospective multicenter observational registry of in-hospital cardiac arrests and resuscitation that collects data according to standardized Utstein definitions.[15] All potential cases are screened by dedicated staff at individual hospitals by reviewing cardiac arrest flow sheets, hospital paging logs, and code cart orders and billing. Data are abstracted from patients' charts by using a universal data collection form and standardized definitions for all data elements. Integrity of data abstraction, accuracy of entries and compliance of operational definitions are ensured through certification of research staff, use of case-study methods and periodic re-abstraction, resulting in a mean error rate of 2.4% for all data. Digital Innovations (Forest Hill, Maryland) acts as a central data repository, removes patient identifiers to ensure confidentiality and compliance with Health Insurance Portability and Accountability Act. Oversight of data collection and analysis, integrity of data, and research is provided by the American Heart Association. The institutional review board of the University of Pittsburgh approved this study and waived the requirement for written informed consent because the data are de-identified and already existed.

2.2. Patient population

Our analysis included sequential data from 355 US and Canadian medical and surgical hospitals that provided data between 1 January 2005 and 7 November 2006. In patients 18 years of age or older, we identified 14,729 cases of in-hospital cardiac arrest that had a resuscitation event and ROSC. Cardiac arrest was defined as cessation of cardiac mechanical activity, determined by the absence of a palpable central pulse, unresponsiveness, and apnea. A resuscitation event was defined as a pulseless cardiopulmonary arrest requiring chest compressions, defibrillation, or both that elicited an emergency resuscitation response by facility personnel and resulted in a resuscitation record. ROSC was defined as a palpable pulse lasting at least 20 min. We excluded those who died or were discharged before 24 h (5234 events) as well as those made Do-Not-Resuscitate (DNR) within 24 h of event (3092 events) to analyze only those patients receiving active post-resuscitation care for the entire period of temperature measurement. We also removed those that had a preceding trauma (126 events) and those with multiple cardiac arrests (72 events). We limited our study population to patients who had an event while in an intensive care unit (ICU), telemetry unit, non-monitored unit, or emergency department (ED). Finally, we included only subjects that had both a lowest (T_{min}) and highest (T_{max}) body temperature value recorded during the first 24-h after ROSC, resulting in a study sample of 3426 patients.

2.3. Body temperature

For our primary analysis, we created categories of body temperature to determine the proportion of study subjects who were able to maintain normothermia versus those who experienced a hyperthermic episode, hypothermic episode, or both in the first 24 h post-arrest. We created temperature categories on the biological basis that the known thermoneutral "set-point" is ~37 °C for humans in health and known diurnal fluctuations in core temperature of ~1 °C.[16–18] Normothermic patients were defined as those who maintained both a T_{min} and T_{max} in the range of 36.0–37.9 °C for 24 h after ROSC. For the purpose of this study, we defined hypothermic patients as those who had a $T_{min} < 36$ °C and a $T_{max} < 38$ °C. Hyperthermic patients were defined as those who had a $T_{max} \geq 38$ °C and a $T_{min} \geq 36$ °C. Those with both a $T_{min} < 36$ and a $T_{max} \geq 38$ °C were defined as having both hyperthermia and hypothermia. In addition, we classified maximum temperature according to the following categories: 36.1–37.0 °C, 37.1–38.0 °C, 38.1–39.0 °C, 39.1–40.0 °C, >40.0 °C.

2.4. Outcome measures

The primary outcome for our analysis was survival to hospital discharge. We also evaluated two secondary outcomes: neurologic and functional status of those who survived to hospital discharge, as measured by the Glasgow-Pittsburgh Outcomes Categories of cerebral performance (CPC) and overall performance (OPC), respectively.[19] Data on these outcomes was available for 89.5% of survivors to hospital discharge. Favorable neurologic and functional performances were defined as a CPC and OPC score of 1 or 2 (range, 1–5) or no change from baseline.[20] A CPC and OPC score of ≥3 represents unfavorable outcome, ranging from severe disability to coma.

2.5. Statistical analysis

We used unadjusted analyses to evaluate the baseline differences between subjects that maintained normothermia and those with an episode of hypothermia, hyperthermia and both in the first 24 h post-ROSC. For continuous variables, we used ANOVA with Bonferroni correction for multiple comparisons or Kruskal–Wallis with post hoc Mann–Whitney *U*-tests. For categorical variables, we used Pearson's chi-square test or Fischer Exact tests. Multivariable models were generated to examine the relationship between individual baseline characteristics and experiencing an episode of hyperthermia.

For our primary analysis we examined the association between body temperature category and outcomes using multivariable models with robust estimation to account for clustering of patients within hospitals. We also performed analyses to explore the relationship between maximum temperature and outcomes. All candidate variables were selected if they were determined to have significant univariate association ($P < 0.05$) with survival. Potential candidates included: age, gender, race (white and black), ethnicity (hispanic and non-hispanic), prior residence (home, acute care hospital, and skilled nursing facility), coexisting medical conditions at the time of arrest, location of arrest (ICU, telemetry unit, and non-monitored unit), first pulseless rhythm (ventricular fibrillation (VF) or pulseless ventricular tachycardia, pulseless electrical activity (PEA) or asystole), witnessed arrest, defibrillation and epinephrine number, and hospital size (<250, 250–500, and >500 inpatient beds). The site of temperature measurement was included as a potential covariate if both T_{min} and T_{max} were taken at the same site, representing 38.4% of all temperature recordings. Coexisting medical conditions include: respiratory insufficiency (within 4 h of event), cardiac arrhythmia any time this admission, renal insufficiency (ongoing dialysis or serum creatinine >2 mg/dl), myocardial ischemia (acute coronary syndrome or infarction) this admission or on prior admission, congestive heart failure this admission or on prior admission, hypotension (SBP < 90 mmHg or MAP < 60 mmHg), diabetes mellitus, pneumonia, septicemia (documented bloodstream infection), cancer, hepatic insufficiency (total bilirubin > 2mg/dl, AST > 2× normal or cirrhosis), and acute stroke (intracranial or intraventicular hemorrhage or thrombus).

Primary outcomes were compared between those who were able to maintain normothermia and those with episodes of