American Journal of Emergency Medicine 35 (2017) 889–892

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Temperature variability during targeted temperature management is not associated with neurological outcomes following cardiac arrest☆,☆☆

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ARTICLE INFO

Article history:
Received 6 December 2016
Received in revised form 19 January 2017
Accepted 26 January 2017

Keywords:
Targeted temperature management (TTM)
Therapeutic hypothermia (TH)
Cardiac arrest
Temperature variability
Cerebral performance category (CPC)

ABSTRACT

Introduction: Recent studies on comatose survivors of cardiac arrest undergoing targeted temperature management (TTM) have shown similar outcomes at multiple target temperatures. However, details regarding core temperature variability during TTM and its prognostic implications remain largely unknown. We sought to assess the association between core temperature variability and neurological outcomes in patients undergoing TTM following cardiac arrest.
Methods: We analyzed a prospectively collected cohort of 242 patients treated with TTM following cardiac arrest at a tertiary care hospital between 2007 and 2014. Core temperature variability was defined as the statistical variance (i.e. standard deviation squared) amongst all core temperature recordings during the maintenance phase of TTM. Poor neurological outcome at hospital discharge, defined as a Cerebral Performance Category (CPC) score > 2, was the primary outcome. Death prior to hospital discharge was assessed as the secondary outcome. Multivariable logistic regression was used to examine the association between temperature variability and neurological outcome or death at hospital discharge.
Results: A poor neurological outcome was observed in 147 (61%) patients and 136 (56%) patients died prior to hospital discharge. In multivariable logistic regression, increased core temperature variability was not associated with increased odds of poor neurological outcomes (OR 0.38, 95% CI 0.11–1.38, $p = 0.142$) or death (OR 0.43, 95% CI 0.12–1.53, $p = 0.193$) at hospital discharge.
Conclusion: In this study, individual core temperature variability during TTM was not associated with poor neurological outcomes or death at hospital discharge.

1. Introduction

Cardiac arrest is a major cause of morbidity and mortality in the United States, affecting approximately 400 000 patients annually and accounting for 15% of all-cause mortality [1,2]. The rate of survival to hospital discharge remains exceedingly low and <10% of cardiac arrest victims are discharged with a favorable neurological outcome [3]. Neurological injury remains the leading cause of death in this patient population and accounts for approximately two-thirds of all-cause mortality [4].

In an effort to minimize ongoing neurological injury, the use of targeted temperature management (TTM) in comatose survivors of cardiac arrest has become the standard of care [5,6]. Modifiable factors with regard to TTM include duration of treatment, mechanism of cooling, rate of rewarming, and target temperatures. There is a paucity of observational data that evaluate most of these variables as prognostic indicators. However, with regard to target temperatures, the argument for more aggressive TTM with lower temperatures was refuted by the findings of a large international randomized trial, which showed no differences in neurological outcome or survival based on a target temperature of 33 °C or 36 °C [7,8].

The effects of temperature variation outside the range of 33–36 °C have only been evaluated in observational studies. There is some

☆ Authorship disclosure: All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
☆☆ Conflicts of interest: No potential conflicts of interest are disclosed. No grant support was used in the preparation of this work.

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http://dx.doi.org/10.1016/j.ajem.2017.01.058
0735-6757/

evidence that hyperthermia in the first 48 h following cardiac arrest is associated with worse neurological outcomes and lower odds of survival [9]. The effects of significant hyperthermia or hypothermia exclusively in patients undergoing TTM following cardiac arrest are not as clear [10]. Moreover, to our knowledge there has been no previous study that evaluates the prognostic significance of continuous variations in core temperatures during TTM. We sought to better characterize core temperature variability during the maintenance phase of TTM and to assess for any relationship between increased temperature variability and neurological outcomes.

2. Methods

2.1. Patient population & study design

The study population included 242 consecutive patients treated at a tertiary care hospital between 2007 and 2014 who met the following criteria: cardiac arrest from non-traumatic etiology, comatose following successful return of spontaneous circulation (ROSC), and treatment with the institution's TTM protocol for at least 24 h. All patients were cooled externally using an active surface-cooling device, the Arctic Sun System, to maintain a core body temperature of 33 °C during the maintenance phase of TTM [11]. This was followed by active rewarming with a goal rate of 0.25 °C per hour.

Following approval from the institutional review board, demographic and clinical data were collected for each patient in a prospective manner and stored in a REDCap database [12]. These variables included age, sex, location of arrest, initial rhythm at time of arrest, receipt of bystander cardiopulmonary resuscitation (CPR), time to ROSC, and Cerebral Performance Category (CPC) scores at hospital discharge. Initial rhythm was assessed as either a shockable [ventricular tachycardia (VT) or ventricular fibrillation (VF)] or non-shockable rhythm. Presence of shock at admission was defined as systolic blood pressures (SBP) <90 or by the use of vasopressors. Mechanical circulatory support was defined as the use of either (1) an intra-aortic balloon pump (IABP), (2) extracorporeal membrane oxygenation (ECMO), or (3) ventricular assist device (VAD). Time to the initiation of TTM and time to reach target temperature were calculated from the time to ROSC. Time at target temperature was calculated via a review of the vital signs in the electronic health record (EHR) to estimate the duration of time each patient's core temperature was maintained at a goal of 33 °C. Troponin I concentrations were recorded where available and are reported as μg/l (normal < 0.05 μg/l).

Each patient's course of TTM was conceptualized in four parts: induction, maintenance, rewarming, and normothermia. The maintenance phase was defined as starting with first core temperature at or below the target and ending with the first attempt at active rewarming. Core temperature variability was defined as the statistical variance (i.e. standard deviation squared) amongst all core temperature recordings during the maintenance phase.

The primary outcome of this study was poor neurological outcome at hospital discharge, defined as a CPC score > 2 [13]. A favorable neurological outcome (neurologically intact survival) was defined as a CPC score of 1 or 2. Death prior to hospital discharge was assessed as the secondary outcome.

2.2. Statistical analysis

All information was de-identified prior to statistical analysis in Stata Statistical Software: Release 14 (College Station, TX, USA) [14]. Descriptive statistics were calculated as the median with interquartile ranges (IQR) for continuous variables. Frequencies (percentages) are depicted for categorical variables. Multivariable logistic regression was used to assess for an association between core temperature variability and neurological outcomes while adjusting for age, location of arrest, receipt of bystander CPR, initial rhythm, initial temperature, time to ROSC, time to TTM, time at target temperature, in addition to maximum and minimum temperatures within 48 h of cardiac arrest. A similar analysis was done to assess the association between core temperature variability and survival to hospital discharge. Odds ratios (OR) with 95% confidence intervals (CI) are presented. All tests were two-tailed and a *p*-value of less than or equal to 0.05 was considered statistically significant.

3. Results

Baseline demographic and clinical characteristics of the cohort are presented in Table 1. The median core temperature during the maintenance was 32.9 °C (IQR 32.4 °C–33.3 °C). Core temperature variability was calculated as the statistical variance amongst core temperature recordings during the maintenance phase of TTM. Amongst all patients, the median variability during the maintenance phase was 0.22 $°C^2$ (IQR 0.08–0.42 $°C^2$). A comparison of core temperature variability with CPC scores at hospital discharge is provided in Fig. 1.

A poor neurological outcome was observed in 147 (61%) patients and 136 (56%) patients died prior to hospital discharge. Multivariable logistic regression was used to test for an association of core temperature variability with poor neurological outcomes and death at hospital discharge. The covariates in the models were age, receipt of bystander CPR, initial rhythm, initial temperature, location of arrest, time spent at target temperature, time to ROSC, time to TTM, and the highest and lowest recorded temperatures within 48 h of arrest. Higher levels of core temperature variability were not associated with poor neurological outcomes at hospital discharge ($p = 0.142$). Advanced age ($p = 0.046$) and increasing time to ROSC ($p < 0.001$) were associated with higher odds of poor neurological outcomes. Shockable rhythms ($p < 0.001$) and in-hospital arrest ($p = 0.036$) predicted lower odds of poor neurological outcomes, Fig. 2. Increased core temperature variability during TTM was not significantly associated with death prior to hospital discharge ($p = 0.193$). Lengthier times to ROSC were associated with higher odds of death ($p < 0.001$). Shockable rhythms ($p < 0.001$) and in-hospital arrest ($p = 0.039$) were associated with lower odds of death, Table 2.

4. Discussion

The primary findings of this observational study are as follows: (1) individual variation in core temperatures amongst patients treated

Table 1
Baseline characteristics. Data are presented as median (IQR) for continuous variables and number (percentage) of patients for categorical variables. N represents the number of non-missing values. CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; T-max, maximum temperature; T-min, minimum temperature; TTM, targeted temperature management.

Characteristic	Overall	N
Age (years)	61 (51–69)	242
Male (%)	145 (60%)	242
In-hospital arrest (%)	44 (18%)	242
Shockable rhythm (%)	131 (56%)	235
Witnessed arrest (%)	190 (79%)	241
Received bystander CPR (%)	121 (50%)	242
Time to ROSC (min)	20 (15–34)	229
Time to initiation of TTM (min)	122 (65–240)	232
Time to reach target temperature (min)	165 (75–270)	242
Initial body temperature (°C)	36 (34.7–36.7)	242
Time at target temperature (h)	21 (18–24)	242
Core temperature variability ($°C^2$)	0.22 (0.08–0.42)	242
T-max within 48 h of arrest (°C)	37.6 (37.2–38.2)	242
T-min within 48 h of arrest (°C)	31.9 (31.5–32.4)	242
ST-segment elevation myocardial infarction (%)	56 (23%)	239
Peak Troponin I (μg/l)	2.74 (0.42–16.94)	232
Coronary angiography (%)	142 (59%)	242
Percutaneous coronary intervention (%)	65 (27%)	242
Shock on admission (%)	95 (39%)	242
Mechanical circulatory support device (%)	37 (15%)	242