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Clinical paper

Body temperature regulation and outcome after cardiac arrest and therapeutic hypothermia☆

Jakobea Benz-Woerner[a], Frederik Delodder[a], Romedi Benz[b], Nadine Cueni-Villoz[a], François Feihl[c], Andrea O. Rossetti[d], Lucas Liaudet[a], Mauro Oddo[a,*]

[a] Department of Intensive Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne University Hospital and Faculty of Biology and Medicine, 1011 Lausanne, Switzerland
[b] Department of Anesthesiology, Luzerner Kantonsspital, 6000 Luzern, Switzerland
[c] Division of Clinical Pathophysiology, CHUV, Lausanne University Hospital and Faculty of Biology and Medicine, 1011 Lausanne, Switzerland
[d] Department of Clinical Neurosciences, CHUV, Lausanne University Hospital and Faculty of Biology and Medicine, 1011 Lausanne, Switzerland

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ABSTRACT

Objective: Therapeutic temperature modulation is recommended after cardiac arrest (CA). However, body temperature (BT) regulation has not been extensively studied in this setting. We investigated BT variation in CA patients treated with therapeutic hypothermia (TH) and analyzed its impact on outcome.

Methods: A prospective cohort of comatose CA patients treated with TH (32–34 °C, 24 h) at the medical/surgical intensive care unit of the Lausanne University Hospital was studied. Spontaneous BT was recorded on hospital admission. The following variables were measured during and after TH: time to target temperature (TTT = time from hospital admission to induced BT target <34 °C), cooling rate (spontaneous BT – induced BT target/TTT) and time of passive rewarming to normothermia. Associations of spontaneous and induced BT with in-hospital mortality were examined.

Results: A total of 177 patients (median age 61 years; median time to ROSC 25 min) were studied. Non-survivors ($N = 90$, 51%) had lower spontaneous admission BT than survivors (median 34.5 [interquartile range 33.7–35.9] °C vs. 35.1 [34.4–35.8] °C, $p = 0.04$). Accordingly, time to target temperature was shorter among non-survivors (200 [25–363] min vs. 270 [158–375] min, $p = 0.03$); however, when adjusting for admission BT, cooling rates were comparable between the two outcome groups (0.4 [0.2–0.5] °C/h vs. 0.3 [0.2–0.4] °C/h, $p = 0.65$). Longer duration of passive rewarming (600 [464–744] min vs. 479 [360–600] min, $p < 0.001$) was associated with mortality.

Conclusions: Lower spontaneous admission BT and longer time of passive rewarming were associated with in-hospital mortality after CA and TH. Impaired thermoregulation may be an important physiologic determinant of post-resuscitation disease and CA prognosis. When assessing the benefit of early cooling on outcome, future trials should adjust for patient admission temperature and use the cooling rate rather than the time to target temperature.

1. Introduction

Therapeutic hypothermia (TH) improves the outcome of comatose patients after cardiac arrest (CA)[1,2] and is recommended by recent post-resuscitation guidelines.[3,4] Although therapeutic temperature modulation is increasingly used, how exactly body temperature (BT) is regulated after CA is only beginning to be elucidated, and the impact of TH on BT regulation has not been extensively studied. Intact central nervous system is required for thermoregulation.[5] Altered thermoregulation is thus frequently observed in patients with primary acute brain conditions, mainly due to hypothalamic dysfunction.[6,7] Multiorgan dysfunction and shock states may also cause dysfunction of BT regulation, due to secondary damage of central and peripheral thermoregulatory pathways.[8,9]

Recently, it has been suggested that low spontaneous BT early following resuscitation from CA may be associated with increased in-hospital mortality.[10,11] However, to our knowledge, no study

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* Corresponding author at: Department of Intensive Care Medicine, CHUV, Lausanne University Hospital and Faculty of Biology and Medicine, Rue du Bugnon 46, BH 08.623, 1011 Lausanne, Switzerland. Tel.: +41 79 556 1246; fax: +41 21 314 3045.
E-mail address: mauro.oddo@chuv.ch (M. Oddo).

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has investigated regulation of BT both in the early phase of post-resuscitation care and during the various phases of induced cooling and examined the impact of BT variations on outcome. We examined this issue in a single-center prospective cohort of adult comatose CA patients treated with TH and monitored with core BT for at least 48 h.

2. Methods

2.1. Subjects

Patients included in this study were part of a prospective observational database of comatose patients who were successfully resuscitated from CA and were treated with TH at the medical/surgical intensive care unit (ICU) of the University Hospital of Lausanne, Switzerland, over a 6-year period (2003–2009). The approval for the study was obtained by the local Institutional Review Board with waiver of informed consent since all interventions were part of standard patient care. All patients were initially admitted to the medical emergency room, where they were immediately managed by emergency department and critical care physicians and, after stabilization, were rapidly transferred to the ICU. Baseline demographics included age, gender, initial arrest rhythm, dichotomized as ventricular fibrillation (VF) vs. non-VF (including asystole and pulseless electrical activity), and the time from collapse to return of spontaneous circulation (ROSC).

2.2. Therapeutic hypothermia

All patients were treated with TH to 32–34 °C for 24 h, according to our local written algorithm and as previously described.[12,13] TH was started immediately after admission to the ICU using ice-cold packs and intravenous ice-cold fluids. A surface cooling technique (Arctic Sun System®, Medivance, Louisville, CO, US) was used to maintain TH. A standardized protocol for sedation, analgesia and paralysis was applied to all patients. Midazolam (0.1 mg/kg/h) and fentanyl (1.5 μg/kg/h) were given for sedation and analgesia. Vecuronium (0.1 mg/kg boluses) was administrated during TH to control shivering. Volume resuscitation and noradrenaline were used to keep mean arterial blood pressure above 70 mmHg. Volume controlled ventilation was applied, aiming to maintain PaO_2 >90 mmHg and $PaCO_2$ between 35 and 40 mmHg. Rewarming was achieved passively by retraction of the surface cooling device, and sedation, analgesia and paralysis were stopped when patient BT was >35 °C. Thus, during rewarming, none of the patients received sedatives, analgesics or paralytics.

2.3. Data collection and processing

Spontaneous BT was recorded on hospital admission in the emerging medical room prior to ICU admission, using a rectal thermometer. Associations between outcome and spontaneous BT were first examined in the entire cohort irrespective of the time of the year and according to the outdoor temperature at the time of CA, categorized in four main periods of the year, *i.e.* March–May, June–August, September–November and December–February. On ICU admission, BT was measured continuously via a bladder thermometer or a central venous catheter (pulmonary artery catheter or arterial catheter, using the PiCCO system) and was recorded at least every 30 min. All ICU BT data were retrieved electronically via a computerized bedside clinical information system (Metavision® IMDsoft). For the purpose of this study, the following parameters were calculated for each patient: (1) *time to target temperature* (TTT), defined as the time from admission to the hospital to achieve induced BT < 34 °C, according to previous studies[14,15]; (2) *cooling rate*, defined as the difference between spontaneous BT and induced BT (34 °C) divided by the TTT (*i.e.* spontaneous BT-34 °C/TTT, expressed in °C/h); (3) *duration of passive rewarming*, defined as the time from the end of cooling to achieve BT of 37 °C. Body temperature values (mean, min, max) during the stable maintenance phase of TH and the post-rewarming normothermic phase (NT) were also calculated.

2.4. Outcome assessment

Associations of spontaneous and induced BT variations with outcome were analyzed using in-hospital mortality as primary outcome endpoint. Secondary endpoint was neurological outcome at discharge and at 3 months, using the cerebral performance categories (CPC), dichotomized as good (CPC 1 = full recovery and CPC 2 = moderate disability) vs. poor (CPC 3 = severe disability, CPC 4 = minimally conscious/vegetative state and CPC 5 = death).[12,13]

2.5. Statistical analysis

Continuous variables are reported as median and interquartile range (IQR), and categorical variables as numbers and percentage. Univariate analyses were conducted with the JMP Software® (SAS Institute Inc., Cary, NC, USA), using Mann–Whitney *U* tests for continuous variables and Fisher exact tests for categorical variables. Multivariable logistic regression was performed using Stata 9 software package (Statacorp LP, College Station, TX): the dependent variable was in-hospital mortality and admission BT, time to ROSC and initial arrest rhythm (dichotomized as VF vs. non-VF) were entered as covariates. Significance was assumed at a level of $p < 0.05$.

3. Results

3.1. Patient characteristics

During the study period, 210 patients with coma after out-of-hospital CA were admitted to our ICU. A total of 33 patients were excluded: 14 patients were not treated with TH, 14 patients died within 48 h and 5 patients had incomplete data. Thus, a total of 177 patients were included in the present study. Baseline patient characteristics are summarized in Table 1.

3.2. Associations between in-hospital mortality and spontaneous body temperature on admission

Associations of spontaneous admission BT and in-hospital mortality are summarized in Table 2. Overall, non-survivors had a lower spontaneous BT on hospital admission than survivors (median 34.5 [IQR 33.7–35.9] °C vs. 35.1 [34.4–35.8] °C, $p = 0.04$). Although there was a trend towards lower temperatures in patients with worse neurological recovery, no statistically significant associations were found between admission BT and neurological outcome both at hospital discharge (median 34.8 [IQR 33.8–35.8] °C in patients with poor vs. 35 [34.4–35.8] °C in those with good outcome, $p = 0.11$) and at 3 months (34.7 [IQR 33.7–35.7] °C vs. 35 [34.4–35.4] °C, $p = 0.17$).

Given seasonal variations of outdoor temperature we also examined the relationship between in-hospital mortality and spontaneous admission BT according to the time of the year in which CA occurred (Table 2). We found that non-survivors had lower spontaneous BT at all time of the year, except in warmest months (June 1st to August 31st), where rather an inverse relationship was seen, *i.e.* non-survivors had higher spontaneous admission BT than survivors.