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Greater temperature variability is not associated with a worse neurological outcome after cardiac arrest☆

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ABSTRACT

Aim: Spontaneous alterations in temperature homeostasis after cardiac arrest (CA) are associated with worse outcome. However, it remains unclear the prognostic role of temperature variability (TV) during cooling procedures. We hypothesized that low TV during targeted temperature management (TTM) would be associated with a favourable neurological outcome after CA.
Methods: We reviewed data from all comatose patients after in-hospital or out-of-hospital CA admitted to our Department of Intensive Care between December 2006 and January 2014 who underwent TTM (32–34 °C) and survived at least 24 h. We collected demographic data, CA characteristics, intensive care unit (ICU) survival and neurological outcome at three months (favourable neurological outcome was defined as cerebral performance category 1–2). TV was expressed using the standard deviation (SD) of all temperature measurements during hypothermia; high TV was defined as an SD >1 °C.
Results: Of the 301 patients admitted over the study period, 72 patients were excluded and a total of 229 patients were studied; 88 had a favourable neurological outcome. The median temperature on ICU admission was 35.8 [34.9–36.9] °C and the median time to hypothermia (body temperature <34 °C), was 4 [3-7] h. Median TV was 0.9 [0.6–1.0] °C and 57 patients (25%) had high TV. In multivariable logistic regression, witnessed CA, ventricular fibrillation/tachycardia and previous neurological disease were independent risk factors for high TV. Younger age, bystander cardiopulmonary resuscitation, shorter time to return of spontaneous circulation, cardiac origin of arrest, shockable rhythm and longer time to target temperature were independent predictors of favourable neurological outcome, but TV was not.
Conclusions: Among comatose survivors treated with TTM after CA, 25% of patients had high TV; however, this was not associated with a worse neurologic outcome.

Introduction

Progress has been made in the management of cardiac arrest (CA).[1] The introduction of modern cardiopulmonary resuscitation (CPR) techniques, early defibrillation and prompt bystander CPR has resulted in a significant increase in the rate of return of spontaneous circulation (ROSC).[2] Nevertheless, outcome after hospital admission is often still poor; in particular, post-anoxic brain injury can result in poor functional outcomes and withdrawal of life-sustaining therapies among more than half of comatose survivors.[3]

Increasing efforts have, therefore, been dedicated to improving post-resuscitation care. Optimization of systemic haemodynamics and mechanical ventilation, prevention of seizures and control of glucose levels appear to be reasonable targets of therapy for such patients.[4–7] In this setting, the use of targeted temperature management (TTM) is a complex and still controversial issue. On the one hand, TTM has been shown to provide neuroprotection after brain ischaemia and the early induction of TTM after a witnessed out-of-hospital CA (OHCA) due to shockable rhythms was associated with improved neurological outcome compared to standard of care.[8,9] On the other hand, a recent clinical trial raised doubts about the appropriate levels of temperature to achieve, with moderate hypothermia (36 °C) being as effective as lower temperatures

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(33 °C).[10] Hence, several issues need to be further clarified to optimize the implementation of TTM in the clinical management of comatose survivors after CA.

Importantly, little is known about the optimal method of temperature control after CA. Some studies showed that endovascular cooling systems were associated with a more rapid time to target temperature, a more stable temperature (i.e., reduced temperature variability with regard to the target temperature) and a reduced risk of overcooling than conventional cooling.[11–13] Despite these potential benefits, CA patients receiving TTM using the endovascular cooling systems had similar outcomes to those treated with other techniques.[14] Moreover, clinical studies have shown that spontaneous alterations in temperature homeostasis (e.g., lower temperature on admission, shorter time to target temperature, resistance to passive rewarming) were associated with worse outcome.[15–17] In a recent study, greater heat generation was associated with better neurologic function.[18] Thus, there exists a gap in the knowledge of the factors associated with the induction and achievement of target temperature that may be important to optimize TTM and potentially increase its beneficial effects in CA patients. None of these studies considered whether high temperature variability during cooling procedures could be associated with poor outcome (e.g., increased risk of adverse effects due to overcooling or reduced neuroprotection because of insufficient hypothermia levels) or good outcome (e.g., as a feature of more preserved temperature homeostasis from less extensive brain damage). Thus, the aim of this study was to evaluate the determinants of temperature variability after CA and its effects on patient outcomes.

Patient and methods

Study population

We reviewed data from all patients admitted to the mixed medico-surgical Department of Intensive Care at Erasme University Hospital (Brussels, Belgium) between January 2007 and January 2014 after successful resuscitation from CA. Patients were included if they survived for at least 24 h after a CA, both occurring in-hospital or out-of-hospital, irrespective of age and who underwent TTM for post-anoxic coma (Glasgow Coma Scale [GCS] score <9). Exclusion criteria were lack of >25% of temperature data over the first 48 h of the ICU stay. The local Ethical Committee approved the study, but waived the need for informed consent because of its retrospective nature.

Post-resuscitation care

In our Department, all patients who are comatose after CA are treated with TTM (target temperature: 33 °C; range: 32–34 °C) for 24 h, according to a standardized protocol. For in-hospital CA, cooling is started immediately after ROSC has occurred, whereas for OHCA, TTM is initiated after hospital admission. Hypothermia is induced with a cold fluid bolus (20–30 ml/kg over 30 min of either NaCl 0.9% or Ringer's lactate solution) and maintained for 24 h using a water-circulating blanket device (Medi-Therm II, Gaymar, USA). Body temperature is initially measured using a rectal temperature probe; in those patients requiring an invasive haemodynamic monitoring device (PiCCO, Pulsion, Munich, Germany), temperature is then recorded using the blood sensor. All patients undergoing TTM receive sedation (midazolam, as a continuous infusion of 0.03–0.1 mg/kg/h) and analgesia (morphine or, in case of renal failure, remifentanil at an equipotent dose of 0.1–0.3 mg/kg/h).[19] For shivering control, neuromuscular blocking agents (NMBAs) are administered in the induction phase (cisatracurium as a bolus of 0.15 mg/kg) and, if needed, as a continuous infusion thereafter (1–3 mcg/kg/min). Rewarming is conducted passively, with a target rate of 0.5 °C/h; if increase in body temperature occurs at <0.2 °C/h, active rewarming g is started. Sedation, analgesia and NMBAs are discontinued when normothermia (>37 °C) is achieved. All patients are kept in a semi-recumbent position (30°); mechanical ventilation is adjusted to target a $PaCO_2$ between 35 and 45 mmHg and a SpO_2 of 94–98%. Trans-oesophageal echocardiography is systematically performed after ICU admission to evaluate cardiac function. Blood glucose levels are kept between 110 and 150 mg/dL using a continuous intravenous insulin infusion. Haemodynamic management includes volume resuscitation, dobutamine and/or noradrenaline, whenever needed, targeting a mean arterial pressure >65–70 mmHg. No specific targets are used for cardiac output, although venous oxygen saturation is considered optimal if >65%.[4] In severe cardiogenic shock, intra-aortic balloon counterpulsation (IABP) or extracorporeal membrane oxygenation (ECMO) are used. Enteral nutrition is initiated as soon as possible after target temperature achievement.

When normothermia has been reached, neurological examination is repeated at least every 4 h. Standard or continuous EEG monitoring is initiated at ICU admission and repeated or used continuously for 48–72 h. Withdrawal of life-sustaining therapies is based on an interdisciplinary decision (also involving family members), taking into account the bilateral absence of the N20 cortical responses to somatosensory evoked potentials (SSEPs), persisting coma with absent motor response or posturing and/or presence of status myoclonus or refractory status epilepticus as signs of extended brain damage.[20]

Data collection

Demographics, co-morbidities, data on CPR (first rhythm, bystander CPR, time to ROSC) were collected in all patients from hospital (if in-hospital) or ambulance (if OHCA) records. Temperature was recorded hourly via the ICU patient data monitoring system (PDMS, Picis Critical Care Manager, Picis Inc., Wakefield, USA). Hospital and ambulance reviews were conducted using an institutional database where all the available documents of patients are stored. Data extraction was performed by one investigator (LN) on a pre-defined datasheet and then was internally verified by another investigator (FST) by a random analysis of at least 20% of studied patients. Previous neurological disease was defined as the presence of ischaemic or haemorrhagic stroke, traumatic brain injury, dementia, epilepsy, multiple sclerosis, Parkinson's disease and/or brain tumour. Shock was defined as the need for vasopressor agents for more than 6 h. We reported the maximal (T_{max}), minimal (T_{min}) and mean (T_{mean}) temperatures as well as the difference between the T_{max} and T_{min} (ΔT) during the cooling period. We also recorded the time to reach a temperature <34 °C (time to target temperature) as well as the time to return to normothermia. Overcooling was defined as at least one temperature measurement <32 °C; undercooling was defined as at least one temperature measurement >34 °C. Temperature variability was expressed using the standard deviation (SD) of all measurements during the hypothermia period. Considering that ranges of target temperature (33 °C) during TTM were ±1 °C, a high temperature variability was arbitrarily defined as an SD >1 °C. As we included only patients with less than 25% of missing values (i.e., a maximum of 6 out of 24 h over the study period without values of body temperature), we did not estimate such missing data but considered only available temperatures in all analyses.

For each patient, the total amounts of midazolam, morphine/remifentanil and cisatracurium was collected and expressed as mg/kg/h. Post-hypothermia fever was defined as a body temperature >38.5 °C for at least 2 h during the 24 h following the return to normothermia.[21] All data were reviewed by two authors (LN