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Clinical paper

Ventricular ectopic burden in comatose survivors of out-of-hospital cardiac arrest treated with targeted temperature management at 33 °C and 36 °C☆

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ABSTRACT

Purpose: Life threatening arrhythmias are increasingly frequent with lower body temperature. While targeted temperature management (TTM) with mild hypothermia following out-of-hospital cardiac arrest (OHCA) is generally considered safe and has been suggested as a potential antiarrhythmic add-on therapy, it is unknown whether the level of TTM affects the burden of ventricular ectopic activity. We sought to assess the ventricular ectopic burden between patients treated with TTM at 33 °C or 36 °C for 24 h.
Methods: Continuous 12-lead digital Holter electrocardiograms performed during the intervention were analyzed blinded to treatment allocation in 115 comatose OHCA-survivors from a single center of the TTM-trial. The main study showed no difference with regards to mortality.
Results: Fifty-eight patients were randomized to 33 °C and 57 to 36 °C. Cardiac arrest characteristics were similar between the groups. The number of isolated ventricular ectopic beats (VEB) per hour was similar at the beginning of the maintenance phase of TTM and decreased over time in both groups (both $p_{time} < 0.001$). The reduction in VEB per hour was significantly affected by target temperature ($p_{interaction} < 0.0001$), with fewer VEB in the 36 °C-group. The total number of isolated, couplets and number of runs of VEB per hour showed similar results, with less ventricular ectopic activity in the 36 °C-group ($p_{interaction} < 0.0001$). Increasing numbers of pre-hospital defibrillations (log2) were associated with a 46% increase in ventricular ectopic activity ($p < 0.01$), adjusted for potential confounders.
Conclusions: Ventricular ectopic activity was reduced in comatose OHCA-survivors treated with TTM at 36 °C compared to 33 °C. Higher numbers of pre-hospital defibrillations were associated with higher incidence of ventricular ectopic activity.

Introduction

Targeted temperature management (TTM) is a guideline supported treatment strategy to mitigate anoxic brain injury following out-of-hospital cardiac arrest (OHCA).[1] However, several questions regarding the efficacy, optimal temperature and timing of TTM have arisen following the non-superior results of the TTM-trial,[2] which found no benefit of targeting 33 °C vs. 36 °C in terms of mortality and neurological function. Current resuscitation guidelines have been updated and now leave option for TTM in a broader range from 32 to 36 °C.[1] As the optimal target temperature remains undetermined, improved knowledge regarding the clinical differences

Abbreviations: CAG, coronary angiography; CPC, Cerebral Performance Category scale; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; LVEF, left ventricular ejection fraction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SOFA, Sequential Organ Failure Assessment; STEMI, ST-elevation myocardial infarction; TTM, targeted temperature management; VEB, ventricular ectopic beats.

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and physiological consequences may guide the treating physician in choosing the optimal individual target temperature.

Accidental hypothermia below 32 °C, as defined by the Swiss staging system,[3] increases the risk of life-threatening ventricular arrhythmias.[4] TTM in the range of 32–36 °C is generally considered safe, though adverse events in the form of impaired coagulation, infections and arrhythmias are often observed.[2,5,6] Recently a case-report was published in which TTM at 33 °C was suggested as a potential antiarrhythmic add-on therapy in a patient with ischemic heart disease, as multiple recurrent episodes of ventricular arrhythmia ceased after induction of TTM.[7] Animal studies have shown mixed results with both decreased arrhythmia susceptibility with moderate hypothermia,[8] and higher prevalence of ventricular ectopic activity,[9] similar to a study in human OHCA survivors comparing TTM at 33 °C with normothermia.[10] The ventricular ectopic burden has been shown associated with increased risk of congestive heart failure and death in the general population,[11] but the prognostic implications of ventricular ectopy in post cardiac arrest care is unknown. Whether the level of TTM affects the burden of ventricular ectopic activity following OHCA including ventricular ectopic beats (VEB) and arrhythmia not leading to cardiac arrest is also not known. We aimed to assess the effect of TTM at 33 °C vs. 36 °C in relation to the burden of ventricular ectopic activity and assess potential predictors and the prognostic value of ventricular ectopic activity.

Materials and methods

Study design and population

The present study was a pre-defined single-center sub-study of the Target Temperature Management trial (TTM-trial) approved by the steering committee.[2] The TTM-trial randomly assigned comatose OHCA patients to a target temperature of either 33 °C or 36 °C. Inclusion criteria were: adult (≥18 years) resuscitated OHCA patients of presumed cardiac cause who remained unconscious (Glasgow Coma Score <8) despite sustained return of spontaneous circulation (ROSC) >20 min. Main exclusion criteria were unwitnessed asystole, a core body temperature <30 °C on hospital arrival and severe shock.

Patient management and data collection

Patients eligible for enrollment in the current sub-study were admitted to the cardiac intensive care units (ICU) at Rigshospitalet, Copenhagen University Hospital. Post cardiac arrest care included sedation, intubation and mechanical ventilation. Propofol and fentanyl were used for sedation and analgesia and titrated to a Richmond Agitation scale score of −4. If shivering occurred, a bolus of a neuromuscular blocking agent was administrated. TTM was actively managed in both target temperature groups by a surface-cooling device. An induction phase to achieve the allocated target temperature was protocoled for 4 h, followed by a 24-h maintenance phase. Active rewarming was performed by no more than 0.5 °C h^{-1} until normothermia at 37 °C was regained. Hemodynamic treatment goals included a central venous pressure of 10–15 mmHg, mean arterial pressure equal to or greater than 65 mmHg and an hourly urine output of more than 1.5 ml kg^{-1}, achieved by administration of crystalloid fluids and vasopressors at the discretion of the treating physician. The vasopressor need was assessed by the cardiovascular subset of the Sequential Organ Failure Assessment score (SOFA).[12] Left ventricular ejection fraction (LVEF) was assessed on day 1 after OHCA in the majority of patients (87%), while the remainder was performed within 4 days in patients still alive.

Eligible patients included in the TTM-trial at Rigshospitalet consisted of 171 OHCA patients. The present Holter monitoring study was initiated 2 months after inclusion of the first patient in the TTM trial, at which time 11 patients had already been enrolled at Rigshospitalet. In 45 patients no Holter monitoring was available for analysis, as technical problems were present in 3 patients, 6 died less than 2 h after reaching the target temperature or due to no available Holter equipment at time of multiple inclusions and equipment repair (Fig. 1). Patients included consisted of 115 patients in whom a high fidelity 12-lead digital ECG (Seer 12, GE Healthcare) recording was performed during TTM. One patient died during the intervention, with data included until time of death. Digital analysis was performed by the Mars Holter analysis system™ (GE Healthcare, Milwaukee, WI) followed by manual validation by a single reviewer. Interobserver agreement was assessed in 10 randomly selected patients × 2 h of Holter recording by a second reviewer, with a mean difference in ventricular ectopic events of 0.23 per hour (95% limits of agreement (−1.79 to 2.25)). In 8 recordings the interpretation of the QRS morphology was unclear and a consultant cardiologist with expertise in clinical electrophysiology reviewed and adjudicated the QRS morphology and rhythm. VEB were categorized as isolated, couplets, bigeminal cycles or as runs of ≥3 VEB. All analyses were performed blinded to TTM allocation.

Ethical approval

The ethics committee of the Capital Region of Copenhagen (H-1-2010-059) and the Danish Data Protection Agency approved the study. Informed consent was obtained from the patient's next of kin and general practitioner in accordance with national legislation and/or from included patients when neurological recovery was made. The TTM-trial is registered at ClinicalTrials.gov (Identifier: NCT01020916) and was conducted in adherence with the Declaration of Helsinki.

Survival status and neurological outcome

The TTM-trial database formed the basis for assessment of survival and neurological outcome.[2] Survival status 180 days after the OHCA was retrieved through the Danish National Patient Register, which holds vital status on all registered Danish citizens. The Cerebral Performance Category scale (CPC) is a five-point scale assessing neurological function following brain damage, ranging from 1 (conscious and alert with normal function/slight disability), 2 (conscious and alert with moderate disability), 3 (conscious with severe disability), 4 (comatose or in persistent vegetative state) and 5 (dead). Assessors blinded to treatment allocation used the CPC-scale for outcome assessment 6 months after OHCA. Neurological outcome was dichotomized into either favorable outcome (CPC 1–2) or unfavorable outcome including death (CPC 3–5) for statistical analyses.

Statistical analysis

Baseline characteristics were presented by mean ± standard deviation (SD) or proportions (%) for normally distributed variables, with differences tested by χ^2-test and Students' *t*-test, as appropriate. Non-normal distributed variables were presented by median and the 25–75 percentile range (Q1–Q3) and compared non-parametrically by Wilcoxon rank sum test. For assessment of ventricular ectopic activity, hourly registrations during the maintaining phase were compared between the TTM-groups using repeated measures mixed models with a random intercept and an unstructured covariance structure. The models included the TTM allocation group, time, and the interaction term between TTM-group and time. The fixed type 3 effect of the interaction between