Resuscitation 89 (2015) 36–42

Contents lists available at ScienceDirect

Resuscitation

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

Clinical Paper

Sinus bradycardia during hypothermia in comatose survivors of out-of-hospital cardiac arrest – A new early marker of favorable outcome?☆

Jakob Hartvig Thomsen[a,*], Christian Hassager[a], John Bro-Jeppesen[a], Helle Søholm[a], Niklas Nielsen[b], Michael Wanscher[c], Lars Køber[a], Steen Pehrson[a], Jesper Kjaergaard[a]

[a] Department of Cardiology 2142, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Denmark
[b] Department of Anesthesia and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden
[c] Department of Thoracic Anesthesiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Denmark

ARTICLE INFO

Article history:
Received 14 November 2014
Received in revised form 9 December 2014
Accepted 22 December 2014

Keywords:
Out-of-hospital cardiac arrest
Therapeutic hypothermia
Target temperature management
Sinus bradycardia
Prognostic factor
Outcome

ABSTRACT

Background: Bradycardia is a common finding in patients undergoing therapeutic hypothermia (TH) following out-of-hospital cardiac arrest (OHCA), presumably as a normal physiological response to low body temperature. We hypothesized that a normal physiological response with sinus bradycardia (SB) indicates less neurological damage and therefore would be associated with lower mortality.
Methods: We studied 234 consecutive comatose survivors of OHCA with presumed cardiac etiology and shockable primary rhythm, who underwent a full 24-h TH-protocol (33 °C) at a tertiary heart center (years: 2004–2010). Primary endpoint was 180-day mortality; secondary endpoint was favorable neurological outcome (180-day cerebral performance category: 1–2).
Results: SB, defined as sinus rhythm <50 beats per minute during TH, was present in 115 (49%) patients. Baseline characteristics including sex, witnessed arrest, bystander cardiopulmonary resuscitation and time to return of spontaneous circulation were not different between SB- and no-SB patients. However, SB-patients were younger, 57 ± 14 vs. 63 ± 14 years, $p < 0.001$ and less frequently had known heart failure (7% vs. 20%, $p < 0.01$).

Patients experiencing SB during the hypothermia phase of TH had a 17% 180-day mortality rate compared to 38% in no-SB patients ($p < 0.001$), corresponding to a 180-day hazard ratio ($HR_{adjusted} = 0.45$ (0.23–0.88, $p = 0.02$)) in the multivariable analysis. Similarly, SB during hypothermia was directly associated with lower odds of unfavorable neurological outcome ($OR_{unadjusted} = 0.42$ (0.23–0.75, $p < 0.01$).
Conclusion: Sinus bradycardia during therapeutic hypothermia is independently associated with a lower 180-day mortality rate and may thus be a novel, early marker of favorable outcome in comatose survivors of OHCA.

1. Introduction

Therapeutic hypothermia (TH) is widely used and has been supported by guidelines as a neuro-protective treatment strategy in comatose survivors of out-of-hospital cardiac arrest (OHCA) for more than a decade.[1,2]

It is recognized that the main cause of short-term mortality in comatose OHCA patients is extensive anoxic neurological injury.[3] Early cerebral prognostication is challenging, especially in the era of TH, where prognostic tools are useful only 72 h after normothermia is obtained.[3,4] Initial shockable rhythm, witnessed arrest, bystander cardiopulmonary resuscitation (CPR) and shorter time to return of spontaneous circulation (ROSC) are known pre-hospital factors associated with favorable outcome, however the accuracy of these circumstances is often uncertain and provide only little prognostic value on the individual level.[4] Early markers of favorable outcome during the post-resuscitation care could be useful in providing information to relatives in the days following the arrest and potentially to guide clinical decision making, prioritizing intensive care resources to the benefit of patients with good chances of

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2014.12.031.

* Corresponding author at: Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen O, Denmark.
E-mail address: jakob@jht.dk (J.H. Thomsen).

http://dx.doi.org/10.1016/j.resuscitation.2014.12.031
0300-9572/

recovery and to avoid futile treatment in cases where a permanent vegetative state can be expected.

While the initial rhythm, shockable vs. non-shockable, is an important prognostic factor[5] also heart rate and cardiac rhythms during the post-resuscitation care may provide prognostic information. Heart rate is known to be of significant prognostic importance in both the general population, patients with known ischemic heart disease, hypertension and heart failure, however the prognostic implications of heart rate in acute circumstances e.g. in OHCA patients during and after TH remains to be established.[6,7]

We hypothesized that a normal physiological response to hypothermia by developing sinus bradycardia (SB) <50 beats per minute (bpm) would be associated with lower mortality as a sign of less neurological damage. We assessed the prevalence of SB during hypothermia and its association to outcome in comatose survivors of OHCA and report the prevalence of common cardiac rhythms throughout the post-resuscitation care.

2. Materials and methods

We retrospectively enrolled consecutive comatose survivors of OHCA with presumed cardiac etiology admitted to a single tertiary heart center in Denmark between 1st June 2004 and 31st October 2010, after the local implementation of TH. The Capital Region of Denmark covers approximately 1.9 million citizens; of those nearly 600.000 live in central Copenhagen. Patients admitted after OHCA to Copenhagen University Hospital, Rigshospitalet were patients suffering cardiac arrest in central Copenhagen along with patients suspected of acute coronary lesions with an indication for acute coronary angiogram.

Patients eligible for inclusion in the present analysis were (1) OHCA with presumed cardiac etiology and shockable initial rhythm; (2) age $\geq$ 18 years; (3) sustained return of spontaneous circulation (ROSC) >20 min; (4) Glasgow Coma Scale $\leq$8 upon arrival in the emergency department or cardiac intensive care unit (ICU), as described elsewhere.[8] If cardiogenic shock were present at time of admission, following the shock trial definition[9] (systolic blood pressure <90 mmHg for >30 min or need for supportive measures or end-organ hypotension), patients were excluded. To ensure comparable data on TH's effect on cardiac rhythms and heart rate, patients who did not reach target temperature (TT) <34 °C or were rewarmed <12 h of achieving TT due to hemodynamic instability were also excluded. Further, patients who died in the rewarming phase and thus never reached a core temperature greater that 36.5 °C were excluded to ensure comparable analysis of the effect of rewarming (Fig. 1). A conservative and watchful waiting approach to withdrawal of care was the clinical practice, and based on CT-scan of the brain, electroencephalography, somatosensory evoked potentials and repeated clinical neurological evaluations when normothermia was reached and sedation was tapered, the decision was left to the treating physician. Active management usually continues for at least 3 days following hypothermia.

2.1. Post-resuscitation care

TH was initiated as soon as possible after admission to the ICU according to guidelines[2] by surface cooling, supplemented by infusion of 30 mL/kg 4 °C Ringer's solution. The induction phase started at time of arrival in the ICU until core temperature was lowered to <34 °C. TH was maintained for 24 h with a TT of 33 °C, defining the hypothermia phase. The rewarming phase began 24 h after reaching TT and ended when core temperature reached $\geq$36.5 °C. Average rewarming rate did not exceed 0.5 °C per hour. The post-hypothermia phase started after rewarming (first temperature recorded $\geq$36.5 °C) and ended 72 h after reaching TT.

The ICU treatment protocol was followed and sought to stabilize the patients hemodynamically and metabolically including goal directed criteria with mean arterial pressure >65 mmHg, central venous pressure of 10–15 mmHg and diuresis >1.5 mL/kg/h. Prophylactic antibiotics (cefuroxime 1.5 g three times a day) were administered to all patients intravenously and adjusted at the discretion of the treating physician. Post-hypothermia fever was not actively managed with anti-pyretic drugs. Patients suspected of acute coronary lesions underwent coronary angiography and primary percutaneous coronary intervention was performed if indicated.

2.2. Data collection

Utstein criteria formed the basis for pre-hospital data collection.[10] Data on core temperature (bladder/esophagus) and cardiac rhythms from telemetry were registered hourly by trained intensive care nurses in the patient data management system (IntelliVue Clinical Information Portfolio, Philips). If more than one rhythm was recorded within 1 h, the potentially more hazardous rhythm was selected by the following sequence: asystole, pulseless electrical activity, ventricular fibrillation (VF), ventricular tachycardia (VT), nodal rhythm, 3rd degree AV-block, 2nd degree AV-block, pace rhythm, atrial fibrillation (AF) or atrial flutter, sinus bradycardia (SB), sinus tachycardia >100 bpm (ST), normal sinus rhythm 50–100 bpm (SR). If no rhythm was registered, last entry was carried forward if the rhythm was SR, SB, ST and AF. Data on heart rate and blood lactate level were acquired similarly. Thus no entries carried forward were used for stratification by occurrence of SB or lowest heart rate recorded. Incident SB, defined as sinus rhythm below 50 bpm at any time during the hypothermia phase of TH, according to the primary hypothesis, was used for stratification of the cohort. The Regional Ethics Committee approved the study protocol with waiver of written informed consent (H-4-2010-FSP), as all interventions were part of standard patient care.

2.3. Outcome

The primary endpoint was 180-day mortality and secondary outcome was favorable 180-day neurological status (Cerebral Performance Category, CPC, 1 and 2), supplemented by descriptive results of the prevalence of cardiac rhythms throughout the TH-phases. Citizens in Denmark have a unique personal identification number and via linkage to the Danish National Patient Register, vital status on all included patients was obtained. However, foreigners alive at discharge were censored, as long-term outcome was unavailable. The 5-point scale CPC formed the basis for neurological evaluation and favorable outcome was defined as CPC 1–2 (sufficient cerebral function for independent activities of daily life), unfavorable outcome as CPC 3–5 (ranges from severe cerebral disability, dependent on daily support to brain death) in agreement with earlier studies in this population.[8] Assessment was performed by two investigators (JBJ and JK) in an outpatient visit more than 6 months post OHCA or by reviewing medical records, blinded to previous outcome assessment and stratification in the present study. A strong inter-observer agreement of 85–100% has previously been reported.[11]

2.4. Statistical analysis

Mean ± standard deviation (SD) or proportions (%) were used for data presentation and differences were tested using χ^2-test and Student's *t*-test, as appropriate. Median and interquartile ranges were used to describe non-normal distributed data and differences tested non-parametrically by Wilcoxon rank sum test. To assess SB and heart rate during hypothermia and the association to