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Clinical paper

Lower heart rate is associated with good one-year outcome in post-resuscitation patients☆

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ABSTRACT

Background: Optimal hemodynamic goals in post-resuscitation patients are not clear. Previous studies have reported an association between lower heart rate and good outcome in patients receiving targeted temperature management (TTM) after out-of-hospital cardiac arrest.
Methods: We analyzed heart rate (HR) and outcome data of 504 post-resuscitation patients from the prospectively collected database of the FINNRESUSCI study. One-year neurologic outcome was dichotomized by the Cerebral Performance Category (CPC) to good (1–2) or poor (3–5).
Results: Of 504 patients, 40.1% (202/504) had good and 59.9% (302/ 504) had poor one-year neurologic outcome. Patients with good outcome had lower time-weighted mean HR during the first 48 h in the ICU (69.2 bpm [59.2–75.1] vs. 76.6 bpm [65.72–89.6], $p < 0.001$) and the first 72 h in the ICU (71.2 bpm [65.0–79.0] vs. 77.1 bpm [69.1–90.1, $p < 0.001$]). The percentage of HR registrations below HR threshold values (60, 80 and 100 bpm) were higher for patients with good neurologic outcome, $p < 0.001$ for all. Lower time-weighted HR for 0–48 h and 0–72 h, and a higher percentage of HR recordings below threshold values were independently associated with good neurological one-year outcome ($p < 0.05$ for all). When TTM and non-TTM patients were analyzed separately, HR parameters were independently associated with one-year neurologic outcome only in non-TTM patients.
Conclusion: Lower heart rate was independently associated with good neurologic outcome. Whether HR in post-resuscitation patients is a prognostic indicator or an important variable to be targeted by treatment, needs to be assessed in future prospective controlled clinical trials.

Introduction

Intensive care after successful resuscitation has developed markedly during last decade [1]. Despite active research around post-resuscitation care, data on optimal hemodynamics of these patients remain scarce [2,3]. Recently, two studies reported that better survival and neurologic outcome was associated with lower heart rate (HR) during therapeutic hypothermia (TH) [4,5]. Both therapeutic temperature management (TTM) and vasoactive medications may have an influence on heart rate. Accordingly, we aimed to test the association of heart rate with one-year neurologic outcome in a large prospective FINNRESUSCI data, including both patients treated with and without therapeutic hypothermia.

Methods

The prospective observational FINNRESUSCI study was conducted in 21 Finnish ICUs between March 2010 and February 2011 [6]. In this present study, we included 504 patients from 20 of the 21 participating ICUs with available heart rate data. All patients with available heart rate recordings were included in this pre-planned sub-study of the FINNRESUSCI-study (flowchart in ESM Fig. 1).

Patients and data collection

The inclusion criteria for FINNRESUSCI study was OHCA, age over 18 years and post-resuscitation care in one of the participating 21 Finnish ICUs. The study protocol was approved by the Ethics

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Committee of Helsinki University Central Hospital [6]. The use of TTM was decided by the local ICU protocols.

Data were collected prospectively and included patient demographics, factors known at resuscitation, and treatment in the ICU.

Routine data (demographics, the International Classification of Diseases [ICD-10] diagnosis, ICU scores, physiologic measures, and outcomes), data on vasopressor and inotrope use, and all arterial blood gas analyses that were drawn during intensive care treatment were collected prospectively to the Finnish Intensive Care Consortium (FICC) database, maintained by Tieto Ltd (Helsinki, Finland).

Heart rate registration was performed in each of the participating ICUs. The data were then collected along with other data to the FICC database. The heart rate data were registered as 2–15 min medians in the respective ICUs. 5 ICUs collected data as 15-min medians, one ICU as 5-min medians while the other 15 ICUs collected heart rate data as 2-min medians. For our analyses the heart rate data retrieved from the FICC database was converted to 10-min medians for data from ICUs using 2–5-min medians and the data in 15-min medians were used for analyses without further filtering. The heart rate of 8 patients (1.6%) could not be retrieved from the database. One of the 21 participating ICUs did not collect hemodynamic data to the database.

Outcome data

A neurologist (M.T.), blinded to ICU care, determined one-year functional outcome with a telephone interview with the patient, next of kin, or caregiver. Functional outcome was classified using the cerebral performance category (CPC) and dichotomized into good [1,2] or poor [3–5,7].

Statistical analyses

Data are presented as percentages or medians with interquartile ranges (IQR). We used a Chi-square test or Fisher's exact test, when appropriate for categorical data and the Mann-Whitney *U*-test, for continuous data.

We identified the heart rate measurements, in addition to the highest and the lowest values during the ICU stay. We calculated the heart rate-time integral for (heart rate value x time of measurement from first measurement in 10 or 15 min medians) for evaluation of total heart rate burden during the first 48 h and the first 72 h in the ICU. By dividing the heart rate-time integral with the aggregate time of the heart rate registrations, we calculated the time-weighted HR values for the first 48 h and 72 h. We identified all values below the following heart rate thresholds: in the ICU during the first 48 h, 60 beats per minute (bpm), 80 bpm, 100 bpm, and calculated the percentage of heart rate registrations during this time interval below these thresholds. We also identified the heart values below heart rate thresholds: 50 bpm, 60 bpm, 70 bpm, 80 bpm, 90 bpm and over 90 bpm, from 500 min to 1500 min from the first heart rate registration in the ICU and assessed the percentage of heart rate registrations below the thresholds, during this time interval.

We analyzed the ability of time-weighted mean heart rate values for 48 and 72 h from ICU admission to predict neurologic outcome for all patients and for TTM or non-TTM treated patients respectively using Area under Receiver Operating Characteristics (ROC) curve (AUCs) with 95% confidence intervals (CI). We estimated the best cut-off value for prediction of one-year outcome of the time-weighted mean heart rate values by Youden index (sensitivity + specificity -1).

We performed a univariable analysis to determine prognostic factors for one-year neurologic outcome. Finally, variables with a p-value $<$ 0.1 were entered in a backward logistic regression analysis to evaluate the possible independent associations between heart rate parameters and one-year outcome for all patients. We performed the regression analyses using the enter method and confirmed by performing a backward stepwise conditional regression analyses. The following variables were entered to the analyses: Presence of coronary artery disease, use of epinephrine during CPR, therapeutic hypothermia in ICU, shockable initial rhythm, time to return of spontaneous circulation (ROSC), witnessed cardiac arrest, SAPS 24 score, history of chronic heart failure, coronary angiography during ICU stay. In each of the five separate regression analysis models, we entered one of the following heart rate variables: (1) time-weighted mean heart rate for the first 48 h in the ICU, (2) time-weighted mean heart rate for the first 72 h in the ICU, (3) percentage of heart rate recordings below 60 bpm (4) percentage of heart rate recordings below 80 bpm, and (5) percentage of heart rate recordings below 100 bpm. We performed the regression analyses for all patients and for TTM and non-TTM patients separately.

All statistical analyses were performed using IBM, SPSS statistics 21.0 and 22.0 (IBM, Armonk, NY, USA) or NCSS 8 (East Kaysville, UT, USA) software.

Results

We analyzed a total of 953,560 heart rate registrations from 504 patients, which were converted to 237,889 10- or 15-min-median heart rate values for the analyses (ESM appendix). The time from OHCA to ICU admission was 119 (90–162) min and the time from OHCA to the first heart rate registration was 129 (100–175) min (median, IQR)

The baseline and demographic data are shown in Table 1 and ESM Table 3. ICU mortality was 107/504 (21.2%), hospital mortality 218/504 (43.3%) and one-year mortality 222/504 (44.0%). Of the 504 patients, 40.1% (202/504) had good neurologic outcome (CPC 1–2), while 59.9% (302/504) had poor neurologic outcome (CPC 3–5) at one year. Of the 281 patients with shockable rhythm, 241 (85.8%) were treated with TH, and of the 223 patients with non-shockable rhythm, 70 (31.4%) were treated with TH.

Of the study patients, 107 patients died in the ICU. Of these, the last heart rate registration was $\leq$48 h in 65 patients and $\leq$72 h in 86 patients, representing death or withdrawal of intensive care during the study period. In 301 patients, the last heart rate registration was done at $\leq$72 h. Of these 301 patents, 147 left the hospital alive and 107 had good one-year outcome, representing patients no more requiring ICU treatment, who were transferred to the ward during the study period.

The heart rate data of patients with good and poor outcome are presented in Table 2, and ESM Table 1. Quartiles of time-weighted mean heart rate and outcome are presented in Fig. 1 (and ESM Fig. 2). All heart rate recordings during first 48 h in ICU stratified to outcome are presented in Fig. 2.

In Receiver Operating Characteristic (ROC) analyses of all patients, the area under curve (AUC) of the time-weighted mean heart rate for the first 48 h was 0.675 (CI 95%, 0.629–0.721) and 0.658 (CI 95%, 0.611–0.705) for the first 72 h. Of the 307 patients with TTM, time-weighted mean heart rate for the first 48 h AUC was 0.707 (CI 95%, 0.629–0.785) and 0.591 (CI 95%, 0.528–0.655) for the first 72 h. Of the 197 patients without TTM time-weighted mean heart rate of first 48 h AUC was 0.712 (CI 95%, 0.634–0.789) and of first 72 h 0.606 (CI 95%, 0.543–0.669).

With Youden analyses, the best cut-of value of time-weighted mean heart rate 48 h for prediction of good one-year neurologic outcome was below 75.0 bpm for all patients, 68.8 bpm for patients with TTM and 76.2 bpm for non-TTM patients.

In multivariable regression analyses (five separate models) lower time-weighted HR for 0–48 h, lower time-weighted HR for 0–72 h, a higher percentage of heart rate recordings below 60 bpm, 80 bpm, and 100 bpm during the first 48 h were all independently associated with good neurological outcome at one year ($p < 0.05$ for all) (Table 3).

When the regression analyses were performed for TTM and non-TTM patients separately, lower time-weighted HR for 0–48 h, lower time-weighted HR for 0–72 h, and lower percentages of heart rate recordings below 80 bpm and 100 bpm during the first 48 h were all independently associated with good neurological outcome in non-TTM