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Clinical paper

Mean arterial pressure and vasopressor load after out-of-hospital cardiac arrest: Associations with one-year neurologic outcome

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ABSTRACT

The aim of the study: There are limited data on blood pressure targets and vasopressor use following cardiac arrest. We hypothesized that hypotension and high vasopressor load are associated with poor neurological outcome following out-of-hospital cardiac arrest (OHCA).
Methods: We included 412 patients with OHCA included in FINNRESUSCI study conducted between 2010 and 2011. Hemodynamic data and vasopressor doses were collected electronically in one, two or five minute intervals. We evaluated thresholds for time-weighted (TW) mean arterial pressure (MAP) and outcome by receiver operating characteristic (ROC) curve analysis, and used multivariable analysis adjusting for co-morbidities, factors at resuscitation, an illness severity score, TW MAP and total vasopressor load (VL) to test associations with one-year neurologic outcome, dichotomized into either good (1–2) or poor (3–5) according to the cerebral performance category scale.
Results: Of 412 patients, 169 patients had good and 243 patients had poor one-year outcomes. The lowest MAP during the first six hours was 47 (inter-quartile range [IQR] 45–49) mmHg in those with a poor outcome and 53 (51–55) mmHg in those with a good outcome ($p < 0.01$), and lowest MAP was independently associated with poor outcome (OR 1.020 per mmHg, 95% CI 1.002–1.038, $p = 0.03$). During the first 48 h the median (IQR) of the TW mean MAP was 80 (78–82) mmHg in patients with poor, and 82 (81–83) mmHg in those with good outcomes ($p = 0.03$) but in multivariable analysis TWA MAP was not associated with outcome. Vasopressor load did not predict one-year neurologic outcome.
Conclusions: Hypotension occurring during the first six hours after cardiac arrest is an independent predictor of poor one-year neurologic outcome. High vasopressor load was not associated with poor outcome and further randomized trials are needed to define optimal MAP targets in OHCA patients.

Introduction

The overall incidence of out-of-hospital cardiac arrest (OHCA) is high: approximately 37 per 100,000 inhabitants in Europe each year.[1] Patients with sudden OHCA have high mortality,[2,3] and a significant proportion of survivors have various degrees of neurologic impairment. After return of spontaneous circulation, cardiac failure and hypotension are common, regularly leading to the use of vasopressor agents.[4] Optimal hemodynamic management in resuscitated patients is unknown and current guidelines conclude that there is insufficient evidence to recommend specific hemodynamic goals.[5,6] European resuscitation guidelines recommend to target the mean arterial pressure to achieve adequate urine

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output (1 ml/kg/h) and normal or decreasing plasma lactate values.[5] American Heart Association guidelines suggest that hemodynamic goals should be directed on individual patients, because different patients may require different MAP to maintain optimal organ perfusion. [5,6]

Previous analyses of hemodynamic management after OHCA have suggested harm from hypotension mainly during the first six hours after return of spontaneous circulation.[4,7] Vasopressors are commonly used after OHCA, but their use has not been evaluated in a randomized controlled trial. A recent systematic review evaluating published data on associations between MAP and outcome in cardiac arrest patients showed considerable variation in MAP targets.[8] Only one study utilized area under the curve analysis or time-weighted analysis which more accurately reflects MAP values over time.[7] Of note, in patients with septic shock, increased vasopressor load has been associated with increased mortality.[9]

In the current study, we studied time-weighted MAP levels and vasopressor load following OHCA. We aimed to assess MAP levels both early during the first 6 h and 48 h after cardiac arrest. We hypothesized that lower MAP levels and/or higher vasopressor load were associated with poor one-year neurologic outcome in OHCA patients treated in the Intensive Care Unit (ICU).

Materials and methods

Twenty-one Finnish ICUs participated in the FINNRESUSCI study conducted from March 1, 2010 to February 28, 2011.[10] Approximately 98% of the Finnish adult population live in the area of these ICUs. The study included 548 patients, all of whom were considered for inclusion in this pre-determined substudy with electronically recorded data on MAP. The inclusion criteria for FINNRESUSCI study was (1) OHCA, (2) age over 18 years, (3) post-resuscitation care in one of the participating 21 Finnish ICUs from March 1, 2010 to February 28, 2011. The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital.

Patients and general data collection

Data were collected prospectively and included patient demographics, factors at resuscitation and treatment in the ICU, including severity of illness with Acute Physiology and Chronic Health Evaluation (APACHE) II scores. We calculated a modified APACHE score excluding cardiovascular points.

Hemodynamic data

In this stubstudy we focused on patients with hemodynamical data collected and validated during the first 6 and 48 h after ICU admission (Supplementary Fig. 1). Hemodynamic and vasopressor data were recorded from patient data monitoring systems by the Finnish Intensive Care Consortium database maintained by Tieto Ltd, Helsinki. We excluded 9 patients who lacked electronic MAP data, 36 patients treated in one ICU without continuous MAP data, and 91 patients with hemodynamic measurements calculated only in 15-minute intervals, thus the final study cohort included 412 patients (Supplementary Fig. 1). Using automated data collection from patient monitors to clinical information systems, capturing the median value for each one-, two- or five-minute interval (depending on the ICU) a total of 1.2 million blood pressure values were documented. We converted all MAP data into 10-minute median values. For patients who died during ICU stay, MAP registrations and vasopressor data were included in the analysis until death.

We calculated aggregate time below different MAP thresholds (50, 55, 60, 65, 70, 75, 80, 85, 90 mmHg). In addition, we calculated the aggregate area below each of those thresholds, determined by the MAP graph over time. We used the receiver operating characteristic (ROC) analysis of the time-weighted MAP to determine the best cut-off value for prediction of one-year outcome. In addition, we performed separate ROC analyses for: (1) shockable vs. non-shockable rhythms, (2) therapeutic hypothermia (TH) treatment (33° C) vs. no TH treatment, and (3) chronic hypertension vs. no chronic hypertension. The accuracy of the ROC analysis is measured by the area under the ROC curve. An area of 1 represents a perfect test and an area below 0.5 is a worthless test. We estimated the best cut-off value of the time-weighted MAP and the highest norepinephrine dose by Youden index (sensitivity + specificity − 1).[11] We determined the highest, mean and total doses of norepinephrine (NE), epinephrine, dopamine and dobutamine. The mean vasopressor load was calculated using the following formula: vasopressor load (μg/kg/min) = norepinephrine (μg/kg/min) + dopamine (μg/kg/min/2) + epinephrine (μg/kg/min) + phenylephrine (μg/kg/min/10).[12]

In this observational prospective study, no recommendations for hemodynamic or vasopressor treatment were given. Instead, National and European Resuscitation Council guidelines, as well as national or local treatment protocols were applied in the participating hospitals. According to Finnish national guidelines a MAP of 70–90 mmHg was recommended in 2010–2011. Norepinephrine was the first vasopressor to be used although the use of vasoactives was directed on individual patient's needs.

Outcome data

A neurologist (M.T.),[10] blinded to ICU care, determined one-year functional outcome with a phone interview with the patient, next of kin or caregiver. Functional outcome was classified using the cerebral performance category (CPC) and dichotomised into good (1–2) or poor (3–5).[10]

Statistical analyses

We performed all statistical analyses using the SPSS software program (IBM SPSS 21.0 and 22.0; IBM, Armonk, NY, USA). Data are presented as percentages or medians with interquartile ranges (IQR). We used a Chi-square test for categorical data and the Mann–Whitney U test for continuous data. We performed a univariable analysis to determine possible risk factors for the one-year survival and neurologic outcome of the OHCA patients. Variables with a p-value < 0.2 were entered into the multivariable models.

All multivariable models included patients' age, presence of coronary artery disease, whether the arrest was witnessed or not, whether bystander cardiopulmonary resuscitation (CPR) was administered, whether the initial rhythm was shockable or non-shockable, whether adrenaline was used or not, time to return of spontaneous circulation (ROSC), APACHE II points without cardiovascular points, use of therapeutic hypothermia (TH), percutaneous coronary intervention during ICU stay, and total vasopressor load. Into these multivariable models, we separately added: (1) time-weighted mean MAP, (2) the lowest MAP level, and (3) total time spent below MAP threshold 70 mmHg. We also depicted the observed and adjusted good one-year outcome by calculating mean 48-h MAP and the total vasopressor load and by dividing these into tertiles. Adjusted one-year outcome was calculated as the proportion between the observed and predicted poor outcome. The predictive ability of variables was studied by calculating ROC curves with their responding area under the curve (AUC). The AUCs were compared by a Delong test.

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