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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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Table 1
Characteristics of out-of-hospital cardiac arrest patients with good or poor one-year neurologic outcome.

Characteristic	Data available (*n*)	All patients *n* = 412	Good outcome *n* = 169	Poor outcome *n* = 243	*p*-value
Gender, % (male)	412	77	79	75	0.26
Age, median (IQR), years	412	63 (55–72)	61 (54–67)	64 (56–73)	<0.01
BMI	395	26 (25–29)	26 (25–29)	26 (24–29)	0.62
Comorbidity					
Hypertension, %	412	40	36	43	0.14
Coronary artery disease, %	412	29	23	34	<0.01
Previous PCI, %	411	6	7	5	0.61
Cardiac bypass surgery, %	411	9	3	6	0.26
Heart failure, %	412	13	9	17	0.03
Diabetes mellitus, %	412	21	18	24	0.14
Resuscitation factors					
Witnessed cardiac arrest, %	412	90	95	86	0.01
Bystander CPR, %	412	53	59	49	0.07
Initial rhythm	412				<0.01
VF, %		58	79	43	
VT, %		1	2	1	
PEA, %		20	7	29	
ASY, %		20	11	27	
Epinephrine given, %	412	67	54	77	<0.01
Time to ROSC, min	409	20 (13–28)	17 (11–23)	23 (15–30)	<0.01
Severity of illness score					
SAPS II points	412	58 (42–69)	43 (34–59)	63 (55–73)	<0.01
Apache II	412	29 (22–34)	18 (13–25)	31 (27–36)	<0.01
Apache II points without cardiovascular components	412	24 (17–29)	26 (22–31)	26 (22–31)	<0.01
SOFA scores					
SOFA	412	9 (7–11)	8 (6–10)	10 (8–12)	<0.01
Cardiovascular SOFA scores	412	3 (2–4)	3 (3–4)	3 (1–4)	0.46
At admission					
MAP	412	61 (56–68)	63 (58–69)	60 (54–67)	<0.01
Norepinephrine, (μg/kg/min)	46	0.10 (0.05–0.20)	0.08 (0.04–0.15)	0.13 (0.06–0.27)	0.09
Epinephrine, (μg/kg/min)	10	0.07 (0.02–0.17)	0.11 (0.02–0.46)	0.03 (0.02–0.13)	0.33
Dopamine, (μg/kg/min)	9	3.35 (1.97–4.28)	3.56 (2.57–4.34)	2.90 (1.88–4.65)	0.73
During ICU stay					
Therapeutic hypothermia,%	412	61	75	49	<0.01
Sedation, %	412	82	92	75	<0.01
Sepsis					
Severe sepsis, %	412	3	2	4	0.18
Septic shock, %	412	2	1	3	0.17
Treatment					
Coronary angiography, %	412	17	28	9	<0.01
PCI, %	412	9	17	2	<0.01

Values are expressed as medians (interquartile ranges) or percentages. The doses of drugs are calculated for those patients who received aforementioned drug during the first 20 min at ICU admission. PCI, percutaneous coronary intervention; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; ASY, asystole; SAPS II, simplified acute physiology score; SOFA, sequential organ failure assessment.

Results

Of 412 patients, 169 (41%) patients had good and 243 (59%) patients had poor one-year outcomes. Eighty-seven patients (21%) died in the ICU and 172 (42%) in the hospital. There were 169 patients whose CPC was 1–2 and 230 patients with CPC 3–5. Differences in patient characteristics, factors at resuscitation, and ICU care between patients with good and poor outcomes are presented in Table 1.

Mean arterial pressure and vasopressor use during the first six hours

Patients with poor one-year neurologic outcome had lower mean and minimum MAP levels than those with good outcome (Table 2). The median of total time spent below MAP 70 mmHg was 31 min in patients with poor outcome and 17 min in patients with good outcome ($p = 0.03$). A MAP cut-off point of 75 mmHg had the best Youden index in prediction of poor one-year outcome (ROC AUC 0.54, CI 95% 0.48–0.60).

Of the 412 patients, 220 (53%) were treated with vasopressors during the first six hours in the ICU (Table 2). Patients with poor one-year outcome did not receive more vasopressors than those with good one-year outcome i.e. 0.02 (IQR 0.21–0.50) mg vs. 0.01 (0.008–0.04) mg ($p = 0.07$). The highest or the mean NE dose was not higher in patients with a poor outcome than those with a good outcome (Table 2). Time below MAP of 70 mmHg had the highest predictive value for poor outcome (data not shown). The AUC of the mean six-hour MAP for predicting good outcome was not found to be different in those with shockable (0.57 95% CI [0.46–0.68]) compared to non-shockable (0.55 95% CI [0.48–0.63]) rhythm ($p = 0.85$), those treated with TH (0.55 95% CI [0.48–0.62]) compared to does not treated with TH (0.53 95% CI [0.43–0.62]) ($p = 0.69$) nor in patients with a history of chronic hypertension (0.53 95% CI [0.44–0.63]) compared to those with no history of chronic hypertension (0.53 95% CI [0.44–0.63]) ($p = 0.24$) (data not shown). The Youden index of the highest NE dose had a cut-off value of 0.16 μg/kg/min for the best prediction of poor one-year outcome (0.57 95% CI [0.49–0.64]).

With multivariate regression analyses TW mean MAP (1.02 [0.99–1.04]), time spent below MAP 70 mmHg (0.99 [0.99–1.01]) and high vasopressor load (Table 3) were not independent predictors of poor long-term outcome (Table 3). The lowest measured MAP was an independent predictor of poor one-year neurologic outcome (OR 1.02 [1.00–1.04], $p = 0.03$) (Table 3). In addition, we added the interaction between hypotension and vasopressor use as a separate variable in all models. With these analyses, we found that the interaction between hypotension and vasopressor use was

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Table 2
Time weighted mean arterial pressure and vasoactive treatments during the first six hours in intensive care unit after out-of-hospital cardiac arrest.

	All patients *N* = 412	Good outcome *N* = 169	Poor outcome *N* = 243	*p*-value
Time-weighted MAP				
MAP mean	85 (84–86)	87 (85–88)	84 (82–86)	0.03
MAP min	59 (58–61)	61 (59–63)	58 (56–60)	<0.01
MAP max	119 (117–121)	120 (117–122)	119 (116–121)	0.87
Total time spent below MAP threshold, minutes				
50 mmHg	3 (1–5)	1 (0–1)	5 (1–8)	<0.01
55 mmHg	4 (2–6)	2 (0.5–3)	6 (2–10)	<0.01
60 mmHg	7 (4–9)	3 (1.3–4)	10 (5–14)	<0.01
65 mmHg	13 (9–16)	6 (3.8–9)	17 (11–23)	<0.01
70 mmHg	25 (20–31)	17 (11.1–23)	31 (23–39)	0.03
75 mmHg	53 (45–60)	41 (31.0–50)	61 (50–72)	0.65
80 mmHg	91 (81–100)	80 (67.3–93)	98 (84–112)	0.20
85 mmHg	135 (124–146)	128 (112.1–144)	140 (125–154)	0.02
90 mmHg	177 (166–188)	173 (155.6–190)	179 (165–194)	<0.01
MAP area under threshold value during the first 6 h				
50 mmHg	28 (6–50)	9 (0–18)	41 (4–78)	0.03
55 mmHg	45 (13–78)	15 (3–27)	67 (12–122)	0.15
60 mmHg	74 (29–118)	26 (8–43)	107 (33–181)	0.13
65 mmHg	124 (65–182)	48 (24–72)	176 (79–274)	0.14
70 mmHg	223 (146–299)	108 (69–148)	302 (175–428)	0.02
75 mmHg	427 (326–529)	260 (187–332)	543 (380–706)	0.08
80 mmHg	804 (668–939)	580 (458–703)	958 (747–1169)	0.39
85 mmHg	1396 (122–1571)	1130 (945–1315)	1580 (1315–1845)	0.40
90 mmHg	2202 (1985–2420)	1912 (1656–2169)	2403 (2083–2724)	0.57
Norepinephrine, *n* (%)	213 (52)	96 (57)	117 (48)	
Max dose (μg/kg/min)	0.10 (0.05–0.18)	0.10 (0.05–0.15)	0.11 (0.04–0.22)	0.10
Mean dose (μg/kg/min)	0.07 (0.04–0.12)	0.06 (0.04–0.10)	0.08 (0.03–0.14)	0.18
Total dose (mg)	0.02 (0.01–0.04)	0.04 (0.008–0.04)	0.02 (0.009–0.043)	0.12
Epinephrine, *n* (%)	12 (3)	2 (1)	10 (4)	
Max dose (μg/kg/min)	0.56 (0.13–2.77)	3.21 (2.87–3.21)	0.37 (0.11–1.35)	0.12
Mean dose (μg/kg/min)	0.46 (0.10–1.26)	2.46 (1.35–2.46)	0.25 (0.08–0.94)	0.06
Total dose (mg)	0.31 (0.01–0.16)	0.13 (0.02–0.13)	0.03 (0.01–0.15)	0.49
Dopamine, *n* (%)	11 (3)	3 (2)	8 (3)	
Max dose (μg/kg/min)	5.10 (4.23–8.89)	5.10 (4.71–12.96)	5.25 (3.72–8.78)	0.50
Mean dose (μg/kg/min)	4.05 (2.89–6.00)	4.08 (4.05–6.79)	3.07 (2.78–5.85)	0.38
Total dose (mg)	0.57 (0.31–0.95)	0.39 (0.31–1.43)	0.64 (0.29–0.91)	0.92
Vasopressor load, *n* (%)	220 (53)	98 (58)	122 (50)	
Max dose (μg/kg/min)	0.11 (0.05–0.22)	0.10 (0.05–0.15)	0.13 (0.05–0.28)	0.04
Mean dose (μg/kg/min)	0.07 (0.04–0.14)	0.06 (0.04–0.11)	0.08 (0.03–0.19)	0.08
Total dose (mg)	0.02 (0.009–0.05)	0.01 (0.008–0.04)	0.02 (0.21–0.50)	0.07
Dobutamine, *n* (%)	56 (14)	26 (15)	30 (12)	
Max dose (μg/kg/min)	2.87 (2.12–3.89)	3.08 (1.98–3.80)	2.72 (2.19–3.92)	0.97
Total dose (mg)	0.75 (0.55–0.91)	0.74 (0.58–0.86)	0.76 (0.44–0.92)	0.88

Values are expressed median (IQR) or count (percentages). The median doses of drugs are calculated for those patients who received aforementioned drug.

Table 3
Factors during the first six hours in the intensive care unit associated with poor one-year outcome in patients with out-of-hospital cardiac arrest by multivariate logistic regression analyses.

Characteristic	Model 1 Odds ratio (95% CI)	*p*-value	Model 2 Odds ratio (95% CI)	*p*-value	Model 3 Odds ratio (95% CI)	*p*-value
Age (per one year)	1.01 (0.99, 1.03)	0.47	1.01 (0.99, 1.03)	0.47	1.01 (0.99, 1.03)	0.51
Previous diagnosis of coronary artery disease	2.96 (1.64, 5.36)	<0.01	2.87 (1.59, 5.18)	<0.01	2.97 (1.64, 5.38)	<0.01
Witnessed cardiac arrest	0.66 (0.28, 1.58)	0.35	0.63 (0.26, 1.52)	0.31	0.65 (0.27, 1.54)	0.33
Bystander CPR	1.17 (0.71, 1.94)	0.55	1.19 (0.72, 1.97)	0.49	1.18 (0.71, 1.97)	0.51
Shockable	0.35 (0.18, 0.68)	<0.01	0.34 (0.18, 0.66)	<0.01	0.35 (0.18, 0.68)	<0.01
Adrenalin	2.52 (1.38, 4.58)	<0.01	2.42 (1.34, 4.39)	<0.01	2.65 (1.44, 4.85)	<0.01
Time to ROSC	1.00 (0.98, 1.03)	0.79	1.00 (0.98, 1.03)	0.82	1.00 (0.98, 1.03)	0.86
Apache II without cardiovascular values	1.09 (1.05, 1.13)	<0.01	1.09 (1.05, 1.13)	<0.01	1.09 (1.05, 1.14)	<0.01
Therapeutic hypothermia	0.44 (0.23, 0.84)	0.01	0.46 (0.24, 0.87)	0.02	0.42 (0.22, 0.81)	0.01
PCI (ICU)	0.50 (0.21, 1.17)	0.11	0.47 (0.20, 1.11)	0.09	0.46 (0.20, 1.10)	0.08
Vasopressor load	1.89 (0.26, 13.59)	0.53	1.92 (0.26, 14.20)	0.52	2.04 (0.29,14.54)	0.48
Time-weighted mean MAP	1.02 (0.99, 1.04)	0.15	–	–	–	–
MAP min	–	–	–	–	1.02 (1.00, 1.04)	0.03
Total time spent below MAP threshold 70 mmHg	–	–	0.99 (0.99, 1.01)	0.51	–	–

Each model was adjusted for age, coronary artery disease, witnessed cardiac arrest, bystander CPR, shockable rhythm, adrenalin, time to ROSC, APACHE II w/o cardiovascular scores, therapeutic hypothermia, PCI and total vasopressor load.

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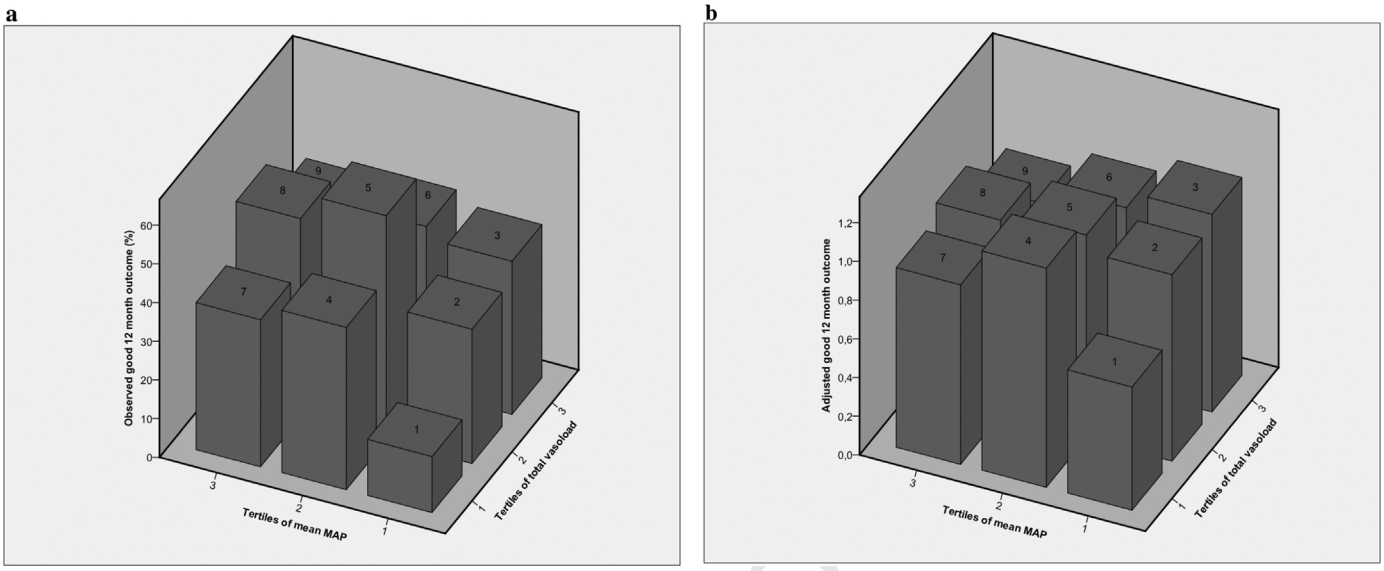

Fig. 1. (a) Tertiles of time-weighted mean arterial pressure and vasopressor load during the first 48 h and observed good one-year neurologic outcome in OHCA patients. (b) Tertiles of time-weighted mean arterial pressure and vasopressor load during the first 48 h and adjusted good one-year outcome after out-of-hospital cardiac arrest. MAP tertiles: 1 = 33–76 mmHg; MAP tertile 2 = 76–84 mmHg; MAP tertile 3 = 84–124 mmHg. Total VL tertiles: 1 = 0–0.04 mg; VL tertile 2 = 0.06–0.13 mg; VL tertile 3 = 0.13–9.97 mg. Number of patients (*n*): (1) *n* = 44; (2) *n* = 32; (3) *n* = 61; (4) *n* = 29; (5) *n* = 58; (6) *n* = 51; (7) *n* = 64; (8) *n* = 48; (9) *n* = 25.

not an independent predictor of long-term outcome ($p = 0.57$–0.65; data not shown).

Mean arterial pressure and vasopressor use during the first 48 h

The mean (80 mmHg vs. 82 mmHg, $p = 0.03$) and the lowest (47 mmHg vs. 53 mmHg, $p < 0.01$) measured MAP levels were lower in patients with poor outcome compared to those with good one-year outcome (Supplementary table* 1). The mean (78 mmHg vs. 80 mmHg, $p = 0.04$) and the lowest (53 mmHg vs 57 mmHg, $p = 0.03$) MAP levels were also lower in TH-treated patients with poor outcome. Interestingly, those with no TH-treatment MAP min ($p = 0.03$) was significant but MAP mean was not (p = 0.57) (Supplementary table* 3). The total time spent below MAP 70 mmHg was higher in patients with a poor outcome compared to those with good outcome (176 min vs. 152 min, $p = 0.03$) (Supplementary Table 1). The Youden index of mean MAP had a cut-off value of 76 mmHg for best prediction of one-year outcome, (ROC AUC 0.56; CI 95% 0.51 to 0.62). The AUC for the mean 48 h MAP for predicting good outcome was not different for patients with shockable rhythm (0.61 95% CI [0.54–0.68]) compared to those with non-shockable (0.51 95% CI[0.41–0.61]) ($p = 0.14$) or patients with chronic hypertension (0.59 95% CI[0.50–0.68]) compared to those without (0.54 95% CI[0.47–0.61]) ($p = 0.46$). The AUC for the prediction of good outcome for mean 48 h MAP was higher in those treated with TH (0.62 95% CI[0.55–0.69]) compared to those not treated with TH (0.49 95% CI[0.36–0.58]) ($p = 0.03$) (data not shown).

Of the 412 patients, 273 (66%) were treated with NE during the first 48 h in the ICU. Patients with poor outcome received higher maximum doses of NE (0.13 μg/kg/min vs. 0.10 μg/kg/min, $p = 0.02$) and higher mean doses of NE (0.07 μg/kg/min vs. 0.05 μg/kg/min, $p = 0.04$) than those with good outcome (Supplementary Table 1). Other details of vasopressor and inotrope treatment are presented in Supplementary table* 1. A comparison of vasopressor load between TH-treated patients and those who did not receive TH-treatment is presented in Supplementary Table 3. The Youden index of the highest NE dose had a cut-off value of 0.12 μg/kg/min for the best prediction of poor one-year outcome (ROC AUC 0.58; CI 95% 0.51–0.65).

With multivariate regression analyses 48-hour TW mean MAP (1.00 [0.98–1.03], $p = 0.90$), minimum 48-hour MAP (1.00 [0.98–1.02], $p = 0.67$), 48-hour TWA-MAP below 70 mmHg (1.00 [0.99–1.01], $p = 0.63$) and total vasopressor load, were not found to be independent predictors of long-term outcome (Supplementary Table 2). Tertiles of the mean 48-hour MAP and vasopressor load with observed and adjusted good one-year neurologic outcome are shown in Fig. 1a and b. Furthermore, we added the interaction between hypotension and vasopressor use as a separate variable in all models and found that this interaction was not an independent predictor of outcome ($p = 0.21$–0.27; data not shown).

Discussion

In this prospective multicenter observational study with high-frequency capture of MAP and vasopressor data, we found that hypotension during the first six hours is an independent predictor of poor outcome after OHCA. Time-weighted MAP was not an independent predictor of outcome. Furthermore, contrary to our hypothesis, we found no association between vasopressor load and poor neurologic long term outcome. Initial rhythm, or treatment with TH or the presence of chronic hypertension did not change the results.

The injured brain is vulnerable to hypotension during the first hours after ROSC, due to reduced brain perfusion and disruption of cerebral autoregulation. Thus maintaining an adequate MAP may be the only way to maintain cerebral perfusion. Studies measuring cerebral blood flow during the post resuscitation period have indicated a clear decrease during the first 24 h after ROSC.[13] Thus, maintaining an adequate MAP might influence the severity of post-resuscitation brain damage and improve neurologic survival. However, to date, the evidence of any association between MAP levels and outcome is inconclusive. The present guidelines for post-resuscitation care of OHCA-patients recommend keeping MAP levels close to the patient's assumed normal level, taking into account the presence of chronic hypertension.[5] In this study, we were unable to confirm any difference in the predictive value of MAP between patients, with or without chronic hypertension.

To the best of our knowledge, previous studies on blood pressure levels and outcome in OHCA patients have been mainly

single-center studies comprising only a limited number of hemodynamic measurements and without data on long-term neurologic outcome.[4,7] In a single-center prospective observational study containing both in-hospital and OHCA patients, Kilgannon and colleagues found that a MAP greater than 70 mmHg during the first six hours after resuscitation was independently associated with good neurologic function at hospital discharge.[7] A recent Australian study showed that the survival rate to hospital discharge of OHCA patients with an initial shockable rhythm was highest with systolic blood pressures (SBPs) between 120 and 129 mmHg on hospital admission and SBPs below 90 mmHg were associated with lower odds of hospital survival.[14] In this study, we did not find any good cut-off value for MAP, the best being 75 mmHg for good outcome but with a very low predictive value. Even though patients with a poor outcome spent longer time below MAP 70 mmHg than those with good outcome, this association between MAP and outcome disappeared with multivariate analysis. Bro-Jeppesen et al. suggested recently that MAP below 65 mmHg was independently associated with increased mortality.[15] They analyzed a smoothing spline plot from a multivariate model with mean MAP intervention and showed that the curve was J-shaped. It is also plausible that the association between MAP and adjusted good outcome is rather reverse-U-shaped, and thus, both very low and very high MAP-values may be related to poor outcome (Fig. 1b).

Some authors have recommended aiming at MAP levels higher than 70 mmHg after cardiac arrest. In one cohort of IHCA and OHCA patients MAP over 100 mmHg during the first two hours of ROSC independently predicted better neurologic recovery at six months after cardiac arrest.[16] In a dog model, neurologic outcome was improved by induced hypertension after resuscitation.[17] Beylin and colleagues concluded that targeting MAP of almost 100 mmHg is associated with better neurologic outcome (defined as CPC 1–2) in post-cardiac arrest patients at hospital discharge.[4] They found that survivors had higher MAPs at 1 h (96 vs. 84 mmHg), at 6 h (96 vs. 90 mmHg), and at 24 h (86 vs. 78 mmHg) than patients with poor neurologic outcome at hospital discharge. We were unable to confirm these findings.

Since hemodynamic instability is common after ROSC, vasoactive agents are frequently used.[18,19] The causes of hypotension after OHCA are likely multifactorial. Post-cardiac arrest syndrome (PCAS), characterized by brain injury, systemic inflammation and myocardial dysfunction, has many features similar to sepsis, such as endothelial activation and release of inflammatory markers.[20] In patients with sepsis, a higher need of vasopressors is associated with disease-related events and increased mortality.[19] Torgensen and colleagues have reported that higher doses of NE during the first 24 h following OHCA were associated with adverse neurologic outcome at day 28.[18] Bro-Jeppesen and colleagues also showed that high doses of vasopressor agents were associated with an increased risk of death from neurological causes.[15] Another recent study also showed that increasing vasopressor support was negatively associated with good neurologic outcome when adjusted for other confounders.[4] In disagreement with these previous findings, we did not find any independent association between high vasopressor load and adjusted poor one-year neurologic outcome.

One obvious strength of this prospective observational multicenter cohort is the inclusion of a majority of OHCA patients treated in the Finnish ICUs during one year. We analyzed more than a million electronically captured and validated MAP values in 10-minute intervals. Finally, we used the long-term neurologic outcome of survivors, evaluated by a neurologist blinded to ICU treatment, as the endpoint. However, we acknowledge that this study has limitations. First, due to the observational nature of the study, the patients were not randomized to treatment groups targeting different MAP values, vasopressors or fluid treatment. Thus, associations do not indicate causality. Second, we excluded whole ICU's in which MAP data was not registered or registered only in 15 min intervals. Thus, we excluded 132 patients who did not meet the data collection norms. This restricts the power of statistical analysis. Third, our data were controlled for known confounders, but it is possible that other unknown confounding factors related to outcome existed. Fourth, this study focused only on two macrocirculatory factors (MAP level and vasopressor load), though persistent alterations of microcirculatory parameters have been suggested to be related to adverse outcome in OHCA patients.[21] Fifth, the association of CVP, lactate levels and urine output may affect the long term outcome after cardiac arrest. However, we were limited with our data and further studies need to elucidate the association of these variables on long-term outcome of OHCA patients. Sixth, therapeutic temperature modulation and drugs used for sedation and analgesia cause hemodynamic stress to the patients and we can't exclude that the need of vasoactives increases for that reason. Finally, we analyzed only MAP and vasopressor data recorded during ICU stay, and no pre-hospital data on MAP and vasopressor use of the OHCA patients were available.

Conclusions

Hypotension occurring during the first six hours after ICU admission was an independent predictor of poor one-year neurologic outcome in OHCA patients in this large prospective observational nationwide study. Contrary to previous studies, high vasopressor load was not associated with poor outcome. Whether the use of vasopressors to target a specific MAP level would have any positive impact on the long-term outcome of OHCA patients requires further studies in an RCT.

Conflict of interest statement

No conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.05.026.

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