


ORIGINAL



Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial

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Abstract

Purpose: We aimed to determine the feasibility of targeting low-normal or high-normal mean arterial pressure (MAP) after out-of-hospital cardiac arrest (OHCA) and its effect on markers of neurological injury.

Methods: In the Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and REsuscitation (COMAC-ARE) trial, we used a 2³ factorial design to randomly assign patients after OHCA and resuscitation to low-normal or high-normal levels of arterial carbon dioxide tension, to normoxia or moderate hyperoxia, and to low-normal or high-normal MAP. In this paper we report the results of the low-normal (65–75 mmHg) vs. high-normal (80–100 mmHg) MAP comparison. The primary outcome was the serum concentration of neuron-specific enolase (NSE) at 48 h after cardiac arrest. The feasibility outcome was the difference in MAP between the groups. Secondary outcomes included S100B protein and cardiac troponin (TnT) concentrations, electroencephalography (EEG) findings, cerebral oxygenation and neurological outcome at 6 months after cardiac arrest.

Results: We recruited 123 patients and included 120 in the final analysis. We found a clear separation in MAP between the groups ($p < 0.001$). The median (interquartile range) NSE concentration at 48 h was 20.6 µg/L (15.2–34.9 µg/L) in the low-normal MAP group and 22.0 µg/L (13.6–30.9 µg/L) in the high-normal MAP group, $p = 0.522$. We found no differences in the secondary outcomes.

Conclusions: Targeting a specific range of MAP was feasible during post-resuscitation intensive care. However, the blood pressure level did not affect the NSE concentration at 48 h after cardiac arrest, nor any secondary outcomes.

Keywords: Arterial pressure, Cardiac arrest, Intensive care, Neuron-specific enolase (NSE), Hypoxic ischemic encephalopathy, Mechanical ventilation

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Introduction

Arterial hypotension is associated with increased mortality and poor neurological outcome after cardiac arrest and resuscitation [1]. The hemodynamic instability during the post-resuscitation period is thought to be caused by a global ischemia–reperfusion injury leading to myocardial stunning [2], a sepsis-like systemic inflammation [3] and adrenal axis suppression [4]. Because of the hypoxic ischaemic encephalopathy (HIE) developing early after the return of spontaneous circulation (ROSC), autoregulation of cerebral blood flow (CBF) may be impaired and cerebral perfusion may become directly dependent on blood pressure [5]. Thus, arterial hypotension after cardiac arrest may lead to cerebral hypoperfusion and increasing epileptic activity, which may aggravate the developing brain damage.

Targeting a specific blood pressure level has been proposed as a treatment strategy after cardiac arrest, but the optimal target remains unknown [6]. During intensive care, the blood pressure can be regulated with fluid infusions and vasoactive agents. In experimental studies, inducing hypertension with vasoactive agents during the post-resuscitation period has been associated with attenuation of HIE and better neurological outcomes after asphyxial cardiac arrest [7]. According to observational human data, higher mean arterial pressure (MAP) is associated with increased survival and better neurological outcomes [1, 8–10]. In addition, a MAP between 87 and 101 mmHg was associated with cerebral oxygenation values considered as optimal [11]. However, the benefit of using vasoactive agents to raise the MAP to a certain level remains controversial. Actually, both low blood pressures and high vasopressor doses have been associated with increased mortality [12]. Importantly, no randomised controlled trials comparing different levels of MAP after cardiac arrest have been performed [6].

Accordingly, we performed a multi-centre, randomised pilot trial to assess the feasibility and the effect on the serum concentration of neuron-specific enolase (NSE) of targeting low-normal or high-normal MAP after OHCA and successful resuscitation. In addition, we investigated the effect of low-normal vs. high-normal MAP on other markers of neurological and myocardial injury, electroencephalography (EEG) and cerebral oxygenation. Our hypothesis was that higher MAP would result in lower NSE concentrations and attenuation of HIE.

Methods

Trial design

We have published the protocol of the Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and REsuscitation (COMACARE) study previously [13]. Briefly, we performed a prospective,

multi-centre, randomised trial with 2³ factorial design. We randomly assigned 123 unconscious, mechanically ventilated patients resuscitated from OHCA to targeting low-normal or high-normal arterial carbon dioxide tension (PaCO₂), normal or moderately elevated arterial oxygen tension (PaO₂) and low-normal or high-normal MAP for the first 36 h at the intensive care unit (ICU). Accordingly, each patient was randomised into one of eight arms, each arm with a different combination of targets for PaCO₂, PaO₂ and MAP. We report the results of the low-normal vs. high-normal MAP comparison here, and the results of the other parts of the study elsewhere in this journal.

Participants

The eligible participants included adults resuscitated from witnessed OHCA with ventricular fibrillation (VF) or ventricular tachycardia (VT) as the initial rhythm. In addition, all of the following inclusion criteria had to be met: (1) return of spontaneous circulation (ROSC) 10–45 min from the onset of cardiac arrest, (2) confirmed or suspected cardiac origin of the arrest, (3) mechanical ventilation upon ICU arrival, (4) markedly impaired level of consciousness defined as no response to verbal commands and Glasgow Coma Scale (GCS) motor score <5 (withdrawal from painful stimuli at best), (5) deferred consent from next of kin possible or likely, and (6) active intensive care and targeted temperature management (TTM) initiated. Patients with confirmed or suspected acute or pre-existing intracranial pathology and/or suspicion of increased intracranial pressure were excluded from the study. In addition, patients with severe oxygenation failure (defined as PaO₂/FiO₂ (fraction of inspired oxygen) <100 mmHg upon arrival at the ICU) or severe chronic obstructive pulmonary disease were excluded. Other exclusion criteria were age <18 or >80 years and pregnancy.

Six ICUs in Finland and one in Denmark participated in the trial. All patients who were resuscitated from OHCA and admitted to one of the participating ICUs were screened for eligibility. Because of the nature of the trial, the patients' unconscious state and the need for a timely intervention, it was not possible to obtain prior informed consent from the participants at the time of randomisation. Therefore, the patients were randomised, and the intervention was initiated at the time of ICU admission. Deferred informed consent from the patients' next of kin was obtained as soon as they were present at the hospital. After the intervention period, informed consent was also obtained from all patients who regained sufficient neurological function for independent decision-making [cerebral performance category (CPC) 1–2]. The study protocol and the deferred consent option were approved

by the research ethics committees of the Northern Savo Hospital District, Finland (decision No. 295/2015) and the Midtjylland region, Denmark (decision No. 1-10-72-163-16). In addition, the trial protocol was approved by the institutional review board at each site.

Interventions

After ICU admission and randomisation, we guided the treating personnel to target low-normal (65–75 mmHg) or high-normal (80–100 mmHg) MAP by using a continuous infusion of noradrenaline as needed. We allowed fluid boluses to treat hypovolemia according to the treating clinicians' preference. If low cardiac output was confirmed or suspected, the use of an inotrope such as dobutamine or levosimendan was allowed. There were no limits to the infusion rates of noradrenalin or inotropes. We did not lower the blood pressure by any means other than sedation and pain medication in order to meet the low-normal MAP target. In cases with MAP exceeding 140 mmHg or detected left ventricular systolic dysfunction, we allowed the use of vasodilating agents to lower the blood pressure according to the treating clinicians' decisions.

In addition to verbal instructions, we used laminated signs designating the intervention targets at the patients' bedside. The intervention was continued for 36 h from ICU admission or until the patient was extubated or ventilation was set to a spontaneous mode. All patients were treated with targeted temperature management (TTM) at 33 °C or 36 °C and sedated as needed. Standard monitoring, care and investigations according to the local protocol of the ICU were used for all patients, including direct blood pressure monitoring via an arterial catheter.

Outcomes

The primary outcome was the NSE serum concentration at 48 h after cardiac arrest. The main feasibility outcome was the difference in MAP between groups targeting low-normal (65–75 mmHg) and high-normal (80–100 mmHg) MAP. The pre-specified secondary outcomes were serum NSE concentrations at 24 h and 72 h after cardiac arrest; serum S100B protein (a biomarker of glial injury) concentrations at 24 h, 48 h, and 72 h after cardiac arrest; plasma cardiac troponin (TnT) concentrations at 24 h, 48 h, and 72 h after cardiac arrest; regional frontal cerebral oxygenation (rSO_2) measured by continuous near-infrared spectroscopy (NIRS) monitoring during the first 48 h after admission to the ICU; results of continuous electroencephalography (EEG) monitoring for the first 48 h after admission to the ICU, interpreted by an experienced senior neurophysiologist blinded to study group allocation; CPC at 6 months after cardiac arrest (CPC 1–2 considered as good outcome and CPC

3–5 as poor outcome), determined by an experienced neurologist blinded to study group allocation; total duration of intensive care; total duration of mechanical ventilation; length of hospital stay; discharge destination and vital status at 30 days after cardiac arrest (dead or alive). Other feasibility outcomes included distribution of values for primary and secondary outcomes, randomised/screened patient ratio, consent rate, data completion rate and duration of recruitment. The pre-defined serious adverse events (SAE) that could be related to the interventions were severe hypercapnia and respiratory acidosis ($PaCO_2 > 10$ kPa and $pH < 7.15$), unexplained brain edema on CT scanning and severe unexplained ARDS (PaO_2/FiO_2 ratio of < 100 mmHg).

Data collection

Baseline data regarding the participants' age, gender, prior health status, and functional capacity, as well as resuscitation details were saved in a web-based study database (Absolute Imaginary Software, Helsinki, Finland). For the first 48 h after ICU admission, all of the monitored vital parameters, including direct blood pressure measurements via arterial cannula, were saved in a medically approved tablet computer (Arbor M1040, Taiwan) connected to the patient monitor with the GE Healthcare S/5 collect software version 4.0. We obtained blood samples for ABG analysis via an arterial cannula and analysed them on-site as part of the routine ICU care. The results of the ABG analysis, corrected to the patient's actual temperature, were entered manually into the web-based study database. The doses of sedative and vasoactive drug infusions were also entered manually into the database. The ventilator settings were exported directly from the ventilators and saved to a USB drive after the intervention or, if this was not possible, entered manually into the electronic database.

We obtained blood samples for the analyses of the NSE, S100B and TnT concentrations upon ICU admission and 24 h, 48 h and 72 h after cardiac arrest. In the Finnish centres, the samples were centrifuged (2000 G, 10 min) and frozen at -70 °C at the hospital laboratory. Determination of NSE, S100B and TnT was performed using a COBAS e601 line (Hitachi High Technology Co, Tokyo, Japan) with an electrochemiluminescent immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany) in January 2018. Because of possible interference with the NSE results, all serum samples were tested for haemolysis using the Roche haemolysis index and all samples with a haemolysis index > 500 mg of free haemoglobin per litre ($n = 7$) were excluded from the NSE analyses. At the Aarhus University Hospital, Denmark, the samples were analysed immediately by the local laboratory using the same kits as those used by the ISLAB laboratory.

We measured the frontal rSO₂ with a Covidien INVOS 5100C device (Covidien Company, USA) with two non-invasive skin sensors attached to both sides of the patient's forehead by a study nurse. The rSO₂ values (approximately 10 measurements per minute) from both sensors were saved to a USB memory stick attached to the device. We calculated the hourly medians of the rSO₂ values of the left channel and used them in the analysis.

Upon the patient's admission to the ICU, continuous four-channel EEG monitoring with a GE Carescape module connected to the monitor (Datex-Ohmeda S/5 or GE B650/B850 depending on the centre) was initiated and continued for 48 h after admission. We saved the EEG data in the tablet computer recording the vital parameters with the GE Healthcare collect software. One senior neurophysiologist blinded to the study group allocations later analysed all the EEG recordings. The EEG recordings were categorised into three groups according to the degree of abnormality (mild, moderate or severe) as proposed by Crepeau et al. [14] at the beginning and at the end of the intervention.

Randomisation

The study centres used a web-based randomisation system. A cryptographically strong random number generator with modulo bias eliminated was used to generate random numbers, and an unbiased Fisher-Yates (Durstensfeld) algorithm was used to shuffle the blocks. The randomisation was stratified according to the target temperature (33 °C or 36 °C). The participants were enrolled and assigned to study interventions by a study nurse or the treating clinician in the ICU. Because of the nature of the interventions, the treating personnel could not be blinded regarding the treatment targets. However, the NIRS monitor screens were not visible to the ICU staff, as NIRS monitoring was not part of the routine post-resuscitation care at the study centres. Moreover, the neurophysiologist analysing the EEG results and the neurologist evaluating the neurologic recovery of the participants were blinded to the study group allocations.

Sample size calculation

Based on a previous cohort of OHCA patients, we expected the mean NSE concentration at 48 h to be close to 17 µg/L, and the standard deviation near 20 µg/L [15]. A study with 39 patients in each arm would have a power of 80%, with the significance set at 0.05, to detect a 50% difference in NSE. Given the possibility of death prior to 48 h and loss of follow-up, we decided to recruit 50% more patients. Therefore, the sample size was set at 120 patients.

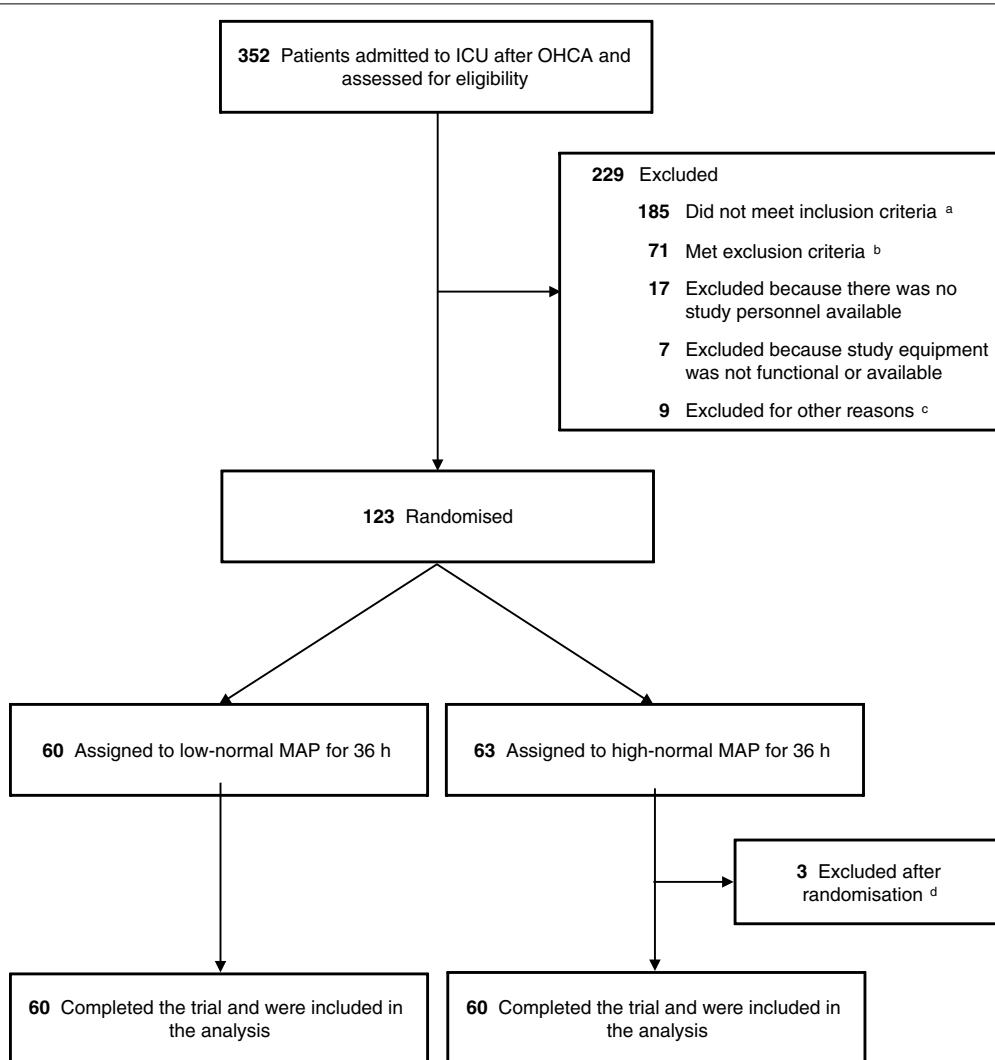
Statistical methods

We compared the categorical data by using the Chi-square test. We tested the normality of the continuous data and compared the data with a normal distribution with the Student's *t* test and the data with a non-normal distribution with the Mann-Whitney *U* test. We divided the intervention time into 1 h periods starting at the time of the ICU admission, and for each patient, we calculated the median MAP for each period. We then compared these 1 h medians for the low-normal and high-normal MAP groups over time using a generalized mixed model with a compound-symmetry covariance matrix. For the low-normal and high-normal MAP groups, we compared the NSE serum concentrations at 48 h using the Mann-Whitney *U* test. We compared the NSE, S100B, TnT and rSO₂ values over time with a generalised mixed model with a compound-symmetry covariance matrix. The distributions of the EEG abnormalities (mild, moderate, or severe), 30-day mortality rates and 6-month CPC results were compared by using the Chi-square test. The interaction effect of the PaCO₂ target and the TTM, PaO₂ and MAP targets on the CPC results at 6 months was analysed with a binary logistic regression model. The interaction of the TTM, PaO₂ and MAP targets on the NSE results at 48 h was assessed with the univariate analysis of variance. We performed all statistical analyses with SPSS version 24.0.

Results

The flowchart demonstrating patient enrollment and group allocation is presented in Fig. 1. The patient recruitment began on 22 March 2016 and was completed by 3 November 2017. The 6-month follow-up of the last patient was completed by 3 May 2018. The baseline characteristics and resuscitation-associated factors were comparable between the groups (Table 1). We observed a clear separation in MAP between the groups, $p < 0.001$ (Fig. 2). The median (inter-quartile range, IQR) noradrenalin dose used was 0.05 µg/kg/min (IQR 0.02–0.11 µg/kg/min) in the low-normal MAP group and 0.13 µg/kg/min (IQR 0.08–0.20 µg/kg/min) in the high-normal MAP group, $p < 0.001$.

The median serum NSE concentration at 48 h after cardiac arrest was 20.6 µg/L (IQR 15.2–34.9 µg/L) in the low-normal MAP group and 22.0 µg/L (IQR 13.6–30.9 µg/L) in the high-normal MAP group, $p = 0.522$. The median NSE, S100B and TnT concentrations and frontal rSO₂ values over time were comparable in the two groups (Figs. 3, 4, 5, 6). We found no significant differences in any of the following outcomes: mortality at 30 days after cardiac arrest, the proportion of patients with good neurological recovery (CPC 1–2)



^a Reasons for not meeting inclusion criteria were as follows: cardiac arrest not witnessed (n=82), initial rhythm other than ventricular fibrillation or ventricular tachycardia (n=104), time to return of spontaneous circulation < 10 or > 45 min (n=62), cardiac arrest with presumed non cardiac cause (e.g. asphyxia, trauma, massive bleeding, aortic dissection, intracranial bleeding) (n=68), patient not mechanically ventilated upon ICU admission (n=7), Glasgow Coma Scale motor score 5-6 (n=45), deferred consent from next of kin not possible or likely (n=17) and active intensive care or targeted temperature management not initiated (n=46).

^b Exclusion criteria met were as follows: withdrawal from active intensive care due to terminal illness or severely reduced functional status (n=19), confirmed or suspected intracranial pathology and/or suspicion of increased intracranial pressure (n=15), age < 18 or > 80 years (n=26), pregnancy (n=1), severe oxygenation disorder at ICU admission (n=26) and severe chronic obstructive pulmonary disease (n=4).

^c Other reasons for exclusion were as follows: long delay (> 6 h) from OHCA to ICU admission (n=3), study personnel was not informed about the patient (n=3), patient died during coronary angiography before ICU admission (n=1), problems with pregnancy test (n=1) and extracorporeal membrane oxygenation initiated at ICU admission (n=1).

^d Reasons for exclusion after randomisation were as follows: deferred consent from next of kin denied (n=2), randomisation error (n=1).

Abbreviations: OHCA, out-of-hospital cardiac arrest; ICU, intensive care unit; MAP, mean arterial pressure.

Fig. 1 Screened, excluded and included patients in the study

Table 1 Baseline characteristics of the study population

	Low-normal MAP group (n=60)	High-normal MAP group (n=60)
Demographic characteristics		
Age, mean \pm SD, years	61 \pm 11	58 \pm 14
Male sex, n (%)	48 (80)	50 (83)
Weight, mean \pm SD, kg	86 \pm 19	83 \pm 14
Neurologic function before cardiac arrest		
Normal, CPC score 1, n (%)	57 (95)	54 (90)
Some disability, CPC score 2, n (%)	3 (5)	6 (10)
Medical history		
Antihypertensive medication, n (%)	26 (43)	34 (57)
Chronic heart failure (NYHA class IV), n (%) ^a	0	2 (3)
Inhaled corticosteroids, n (%)	4 (7)	2 (3)
Inhaled bronchodilators, n (%)	5 (8)	3 (5)
Smoker, n (%) ^b	20 (33)	20 (33)
Cardiac arrest location		
Home, n (%)	32 (53)	28 (47)
Public place, n (%)	28 (47)	32 (53)
Resuscitation factors		
Bystander-initiated resuscitation, n (%)	51 (85)	47 (78)
Time to basic life support ^d , median (IQR), min	8 (6–10)	7 (5–9)
Time to advanced life support, median (IQR), min	10 (7–12)	10 (7–12)
Time to ROSC, median (IQR), min	22 (16–27)	19 (15–25)
Intubated during resuscitation, n (%)	26 (43)	31 (52)
Immediate interventional cardiology		
Pre-hospital thrombolysis, n (%)	3 (5)	1 (2)
Coronary angiography before ICU admission, n (%)	35 (58)	28 (47)
Clinical status on ICU admission		
GCS after ROSC, median (IQR) ^c	3 (3–3)	3 (3–3)
APACHE II score, median (IQR)	28 (24–32)	27 (24–31)
Pre-hospital cooling, n (%)	4 (7)	6 (10)
Dose of norepinephrine, mean \pm SD, μ g/kg/min	0.06 \pm 0.08	0.08 \pm 0.11
Time from ROSC to randomisation, median (IQR), min	171 (148–214)	172 (128–204)
Targeted temperature management		
33 °C, n (%)	42 (70)	41 (68)
36 °C, n (%)	18 (30)	19 (32)

SD standard deviation, IQR inter-quartile range, CPC cerebral performance category [1 good cerebral performance (normal life); 2 moderate cerebral disability (disabled but independent); 3 severe cerebral disability (conscious but disabled and dependent); 4 coma or vegetative state (unconscious); 5 brain death]; NYHA New York Heart Association, CPR cardiopulmonary resuscitation, ICU intensive care unit, GCS Glasgow coma scale, ROSC return of spontaneous circulation, APACHE acute physiology and chronic health evaluation

^a Data missing for two patients

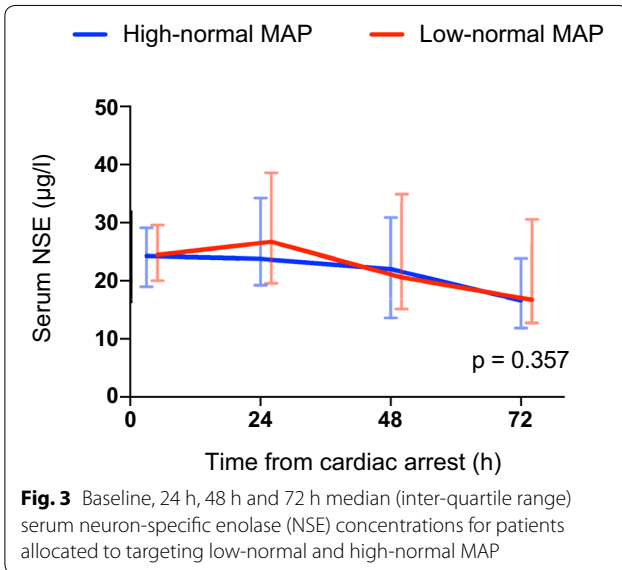
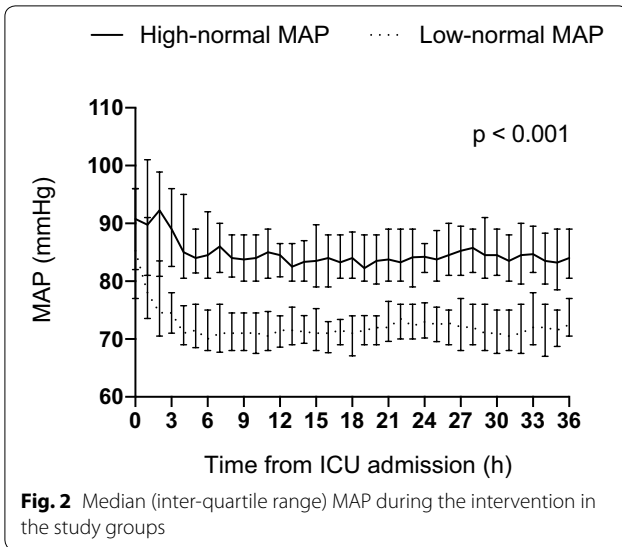
^b Data missing for 13 patients

^c Data missing for nine patients

^d The time for a paramedic unit with BLS equipment and skills to reach the patient

at 6 months after cardiac arrest, the duration of intensive care or mechanical ventilation (Table 2), EEG grading (Table 3) or the frequency of the pre-defined serious adverse events between the groups (Table 2).

Regarding the NSE results at 48 h after cardiac arrest or good neurological outcomes at 6 months, we did not find any significant interactions between the PaCO₂, PaO₂, MAP or TTM targets (online Table 4).



Discussion

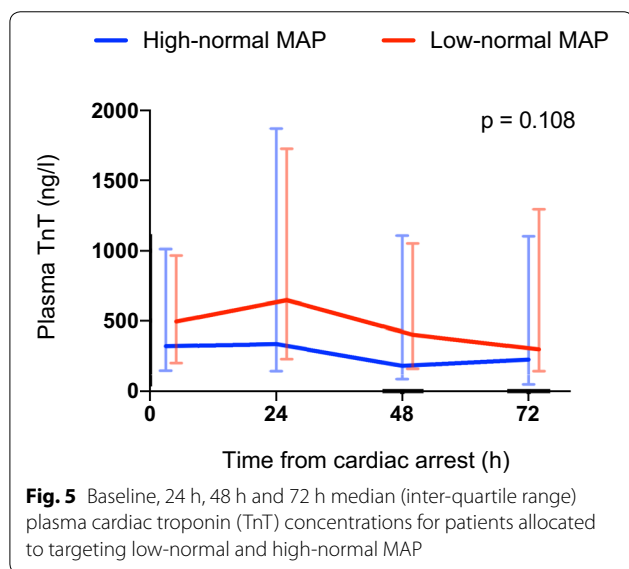
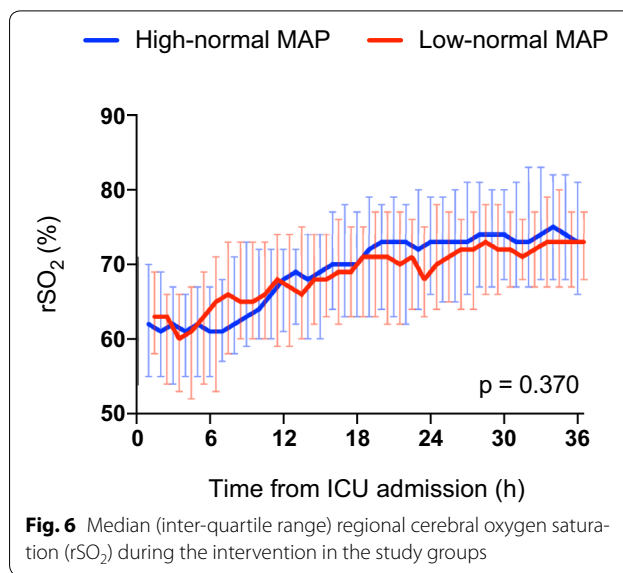
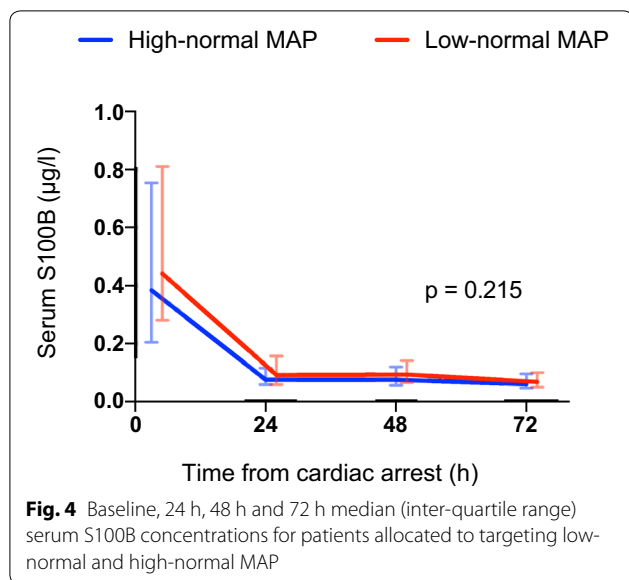
We performed the first prospective, randomised clinical trial assessing the feasibility of targeting low-normal or high-normal MAP after OHCA and successful resuscitation. We compared the effects of low-normal vs. high-normal MAP on biomarkers of brain injury, myocardial injury, brain oxygenation and epileptic activity during the post-resuscitation intensive care. We found that targeting a specific level of blood pressure by using vasoactive infusions was feasible in comatose patients after cardiac arrest. However, a higher MAP level of 80–100 mmHg did not affect the serum concentration of NSE at 48 h after cardiac arrest, when compared with a lower MAP level of 65–75 mmHg. In addition, we found no effects

of higher MAP on the secondary outcomes that included the serum concentration of S100B, the plasma concentration of TnT, brain oxygenation measured with NIRS and epileptic activity on the EEG.

According to observational studies, higher mean arterial pressures are associated with better outcomes, with thresholds of 70 mmHg [16] and 75 mmHg [17] presented. However, treatment recommendations cannot be given on the basis of observational studies alone, because high doses of vasopressors used to raise blood pressures may also be harmful [18]. Because of the lack of high-quality data from randomised trials, current guidelines do not give any specific target for the blood pressure after cardiac arrest, but instead recommend aiming for a blood pressure that is sufficient to achieve an adequate urine output (1 mL/kg/h) and normal or decreasing plasma lactate levels [6]. It is also unclear whether optimal MAP targets differ according to the target temperature, even though hypotension appears to be harmful irrespective of temperature [9]. In our randomised clinical trial, the results in the higher MAP (80–100 mmHg) group were comparable to those in the lower MAP (65–75 mmHg) group concerning all predefined study endpoints. Importantly, our study included patients treated in either 33 °C or 36 °C, and we found no interaction effect of the temperature target and the MAP level.

It has been suggested that the autoregulation of CBF is disturbed after cardiac arrest because of the developing brain damage and that cerebral perfusion may become directly dependent on cerebral perfusion pressure, which is dependent on MAP [5]. Thus, it is plausible that increasing the blood pressure might increase cerebral perfusion and improve oxygenation. However, the results of our trial do not support this hypothesis: cerebral oxygenation, as measured by NIRS, was unaffected by the MAP level. Our findings are in accordance with the results of a previous study in 10 cardiac arrest patients, where increasing MAP from 70 to 90 mmHg did not affect brain tissue oxygenation [19].

The rather small sample size in our trial limits the strength of conclusions that can be drawn. Nonetheless, the fact that we found no signals suggesting either benefits or harms from raising the MAP target from 65–75 to 80–100 mmHg gives little encouragement to the planning of larger trials using these MAP targets and these endpoints. However, it is possible that the optimal MAP may differ between patients, based on their previous blood pressure level and other health factors. Therefore, rather than using the same target for all patients, we may need to estimate the optimal MAP for each patient [20]. The best way to determine the adequate MAP target is unknown so far. Combining continuous transcranial Doppler ultrasound with NIRS might have provided



additional information of the CBF, but for practical reasons it was impossible to implement in this multicentre trial.

Increased epileptiform EEG activity is a predictor of poor outcome after cardiac arrest, but previous studies have not identified any association with blood pressure level and EEG activity [21]. We found that a higher MAP level of 80–100 mmHg did not affect the EEG findings when compared with a lower MAP level of 65–75 mmHg which supports the results of previous observational studies.

Myocardial damage caused by acute coronary syndrome and myocardial ischaemia–reperfusion injury is

common after cardiac arrest and resuscitation. Excessive vasopressor use may lead to increased afterload and increased oxygen consumption of the heart, thereby aggravating the myocardial damage. On the other hand, hypotension or even low-normal blood pressure at hospital admission is associated with increased mortality in patients with acute myocardial infarction [22]. In addition, hypotension can decrease coronary perfusion pressure leading to myocardial hypoperfusion and ischaemia and, eventually, cardiovascular collapse [23]. In our study, the concentration of TnT was comparable in both intervention groups suggesting that there was no difference in the extent of myocardial damage between the groups despite the different blood pressure levels and significantly higher noradrenalin load in the high-normal MAP group.

This study has several strengths. First, we had published the study protocol and the plan for the statistical analysis in advance [13]. Second, we used relatively strict eligibility criteria to focus the trial on a homogenous group of OHCA patients in order to reduce the bias caused by possible differences in baseline characteristics and resuscitation-related factors. Third, we recorded the arterial pressure of the patients continuously for the whole intervention period and modified the infusion rates of vasoactive agents as needed to keep the blood pressure in the desired range. Fourth, we carried out post-resuscitation intensive care according to the current guidelines for all patients. Fifth, we studied patients in multiple centres and two different countries. Sixth, we included patients treated with TTM at both 33 °C and 36 °C. Seventh, we recorded frontal rSO₂ and EEG continuously during the first 48 h of ICU care. Finally, we consider our results

Table 2 Primary and secondary outcomes after the intervention

	Low-normal MAP group (n = 60)	High-normal MAP group (n = 60)	p value
Primary outcome			
Median (IQR) NSE at 48 h after cardiac arrest, µg/L ^a	21.2 (15.1–34.9)	22.0 (13.6–30.9)	0.392
Secondary outcomes			
Neurologic recovery at 6 months after cardiac arrest			
Good, CPC score 1–2, n (%)	37 (62)	41 (68)	0.444
Mortality 30 days after cardiac arrest, n (%)	20 (33)	18 (30)	0.695
Median (IQR) duration of intensive care, h ^b	107 (76–162)	94 (75–136)	0.283
Median (IQR) duration of mechanical ventilation, h ^c	82 (52–123)	59 (49–88)	0.074
Severe adverse events			
Severe hypercapnia and respiratory acidosis (PaCO ₂ > 10 kPa and pH < 7.15), n (%)	1 (2)	0 (0)	0.315
Unexplained brain edema on CT scanning, n (%)	1 (2)	0 (0)	0.315
Severe ARDS (PaO ₂ /FIO ₂ < 100 mmHg), n (%)	2 (3)	0 (0)	0.154

MAP mean arterial pressure, IQR inter-quartile range, NSE neuron-specific enolase, CPC cerebral performance category [1 good cerebral performance (normal life); 2 moderate cerebral disability (disabled but independent); 3 severe cerebral disability (conscious, but disabled and dependent); 4 coma or vegetative state (unconscious); 5 brain death], CT computed tomography, ARDS acute respiratory distress syndrome, FIO₂ fraction of inspired oxygen

^a Data missing for one patient

^b Data missing for six patients

^c Data missing for three patients

Table 3 EEG grading in the low-normal and high-normal MAP groups at ICU admission and at the end of the intervention

	N (%) of patients			
	ICU admission		End of intervention	
	Low-normal MAP	High-normal MAP	Low-normal MAP	High-normal MAP
EEG-grade ^a				
1	12 (20)	19 (32)	39 (65)	39 (65)
2	2 (3)	3 (5)	3 (5)	4 (7)
3	45 (75)	37 (62)	17 (28)	16 (27)
p value	0.278		0.917	

EEG electroencephalography, MAP mean arterial pressure, ICU intensive care unit

^a EEG grading system for continuous EEG findings following cardiac arrest according to Crepeau et al.: mild (grade 1), moderate (grade 2) and severe (grade 3)

reliable because of a clear separation between the study groups in recorded MAP values that were close to the targeted levels.

We acknowledge that this study also has some limitations. First, despite multiple centres participating in the trial, a majority of the patients were recruited in one hospital. Second, as arterial pressure is an important monitored variable for all patients in the ICU, the study intervention could not be blinded, and the treating personnel were aware of the study group allocations. Third, for practical reasons, we decided to start the interventions at the hospital after ICU admission and not during pre-hospital care. We are aware that interventions aiming at affecting the course of HIE should be started as early

as possible. However, we feel that the delay between the ROSC and the beginning of the interventions was acceptable for most participants (Table 1). Fourth, we used a four-channel technique for EEG monitoring and there is a risk that some focal epileptic discharges may have been undetected. Finally, the blood samples taken at the Danish site had to be analysed on-site for logistical reasons. However, to minimise a possible bias resulting from technical issues, we used the same laboratory kits for NSE and S100B evaluation in both Finland and Denmark.

Conclusions

Targeting low-normal or high-normal MAP was feasible in comatose patients resuscitated from OHCA and

admitted to ICU. However, the blood pressure level did not affect markers of cerebral or myocardial injury, cerebral oxygenation, or EEG findings.

Other information

Registration

ClinicalTrials.gov, NCT02698917. Registered on 26 January 2016.

Protocol

The protocol of the COMACARE study has been previously published.

Electronic supplementary material

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