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CARBON DIOXIDE, OXYGEN, AND BLOOD PRESSURE AFTER CARDIAC ARREST AND RESUSCITATION

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ACADEMIC DISSERTATION

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II Jakkula P, Pettilä V, Skrifvars MB, Hästbacka J, Loisa P, Tiainen M, Wilkman E, Toppila J, Koskue T, Bendel S, Birkelund T, Laru-Sompa R, Valkonen M, and Reinikainen M. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Medicine*. 2018; 44:2091–2101.

III Jakkula P, Reinikainen M, Hästbacka J, Loisa P, Tiainen M, Pettilä V, Toppila J, Lähde M, Bäcklund M, Okkonen M, Bendel S, Birkelund T, Pulkkinen A, Heinonen J, Tikka T, and Skrifvars MB. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. *Intensive Care Medicine*. 2018; 44:2112–2121.

IV Jakkula P, Hästbacka J, Reinikainen M, Pettilä V, Loisa P, Tiainen M, Wilkman E, Bendel S, Birkelund T, Pulkkinen A, Bäcklund M, Heino S, Karlsson S, Kopponen H, and Skrifvars MB. Near-infrared spectroscopy after out-of-hospital cardiac arrest. *Critical Care*. 2019; 23:171.

V Ameloot K, Jakkula P, Hästbacka J, Reinikainen M, Pettilä V, Loisa P, Tiainen M, Bendel S, Birkelund T, Belmans A, Palmers PJ, Bogaerts E, Lemmens R, De Deyne C, Ferdinande B, Dupont M, Janssens S, Dens J, and Skrifvars MB. Optimum blood pressure in patients with shock after acute myocardial infarction and cardiac arrest. *Journal of the American College of Cardiology*. 2020; 76:812-824.

Abbreviations and definitions

ABG	arterial blood gas
ACS	acute coronary syndrome
AMI	acute myocardial infarction
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	acute respiratory distress syndrome
CA	cardiac arrest
CBF	cerebral blood flow
CO	cardiac output
CO_2	carbon dioxide
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
EEG	electroencephalography
EMS	emergency medical service
$EtCO_2$	end-tidal carbon dioxide
FiO_2	fraction of inspired oxygen
Hb	haemoglobin
HIE	hypoxic ischaemic encephalopathy
ICP	intracranial pressure
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IQR	interquartile range
MAP	mean arterial pressure
MRI	magnetic resonance imaging
MV	minute ventilation
NIRS	near-infrared spectroscopy
NSE	neuron-specific enolase
OHCA	out-of-hospital cardiac arrest
OR	odds ratio
$PaCO_2$	arterial carbon dioxide tension

PaO_2	arterial oxygen tension
PEA	pulseless electrical activity
ROS	reactive oxygen species
ROSC	return of spontaneous circulation
RR	respiratory rate
rSO_2	regional oxygen saturation
SAE	serious adverse event
SD	standard deviation
SPECT	single-photon emission computed tomography
SpO_2	peripheral oxygen saturation
S100B	S100 calcium-binding protein B
TnT	cardiac troponin T
TTM	targeted temperature management
TV	tidal volume

Abstract

Aims

The objective of this study was to determine the feasibility of targeting low-normal or high-normal arterial carbon dioxide tension ($PaCO_2$), normoxia or moderate hyperoxia, and low-normal or high-normal mean arterial pressure (MAP) in comatose patients after out-of-hospital cardiac arrest (OHCA) and successful resuscitation. In addition, we assessed the effects of the two different levels of $PaCO_2$, arterial oxygen tension (PaO_2) and MAP on markers of neurological and myocardial injury, cerebral oxygenation, and epileptic activity. Moreover, we investigated the association between cerebral oxygenation and the extent of cerebral injury as assessed with markers of brain injury and neurological outcome.

Materials and methods

In the Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and REsuscitation (COMACARE) trial with 2^3 factorial design, 123 patients resuscitated from OHCA with a shockable initial rhythm were randomly assigned to targeting low-normal (4.5–4.7 kPa) or high-normal (5.8–6.0 kPa) $PaCO_2$, normoxia (PaO_2 10–15 kPa) or moderate hyperoxia (PaO_2 20–25 kPa), and low-normal (65-75 mmHg) or high-normal (80-100 mmHg) MAP during the first 36 h in the intensive care unit. The primary outcome was the serum concentration of neuron-specific enolase (NSE) at 48 h after cardiac arrest (CA). Secondary endpoints included NSE concentrations at 24 and 72 h after CA; S100 calcium-binding protein B (S100B) and cardiac troponin T (TnT) concentrations at 24, 48, and 72 h after CA; clinically significant changes in continuous electroencephalography (EEG), results of frontal regional oxygen saturation (rSO_2) measured with near-infrared spectroscopy (NIRS) during the first 48 h of intensive care; and neurologic outcome at 6 months (Studies II-III).

In a post hoc analysis, we evaluated the association between frontal rSO_2 and NSE concentration at 48 h, and the association between frontal rSO_2 and good (Cerebral Performance Category [CPC] 1-2) and poor (CPC 3-5) neurological outcome (Study IV). In another post hoc analysis, we combined data from a subgroup of patients with acute myocardial infarction (AMI) and vasopressor dependent hypotension with data from a comparable subgroup of another trial (Neuroprotect) to evaluate the association between MAP and myocardial injury assessed with the area under the 72-hour TnT curve (Study V).

Main results

We observed a clear separation between the study groups in $PaCO_2$, PaO_2, and MAP during the 36-hour intervention period. However, there was no difference in serum NSE concentrations between the intervention groups at any of the studied time points. S100B and TnT concentrations, EEG findings, and neurological outcome at 6 months were comparable between the groups.

High-normal $PaCO_2$ and moderate hyperoxia significantly increased frontal rSO_2, but MAP level did not. No significant association between frontal rSO_2 and NSE or neurological outcome was observed. In a subgroup of patients with AMI and vasopressor dependent hypotension, combined from the two trials (COMACARE and Neuroprotect), myocardial injury was significantly lower in patients assigned to the higher MAP group. The risk of new-onset CA or arrhythmias was not increased despite significantly higher doses of noradrenaline and dobutamine in the higher MAP group.

Conclusions

Targeting low-normal or high-normal $PaCO_2$, normoxia or moderate hyperoxia, and low-normal or high-normal MAP was feasible in comatose patients after OHCA and successful resuscitation. None of the studied interventions affected the extent of the developing brain damage as measured with biomarkers of neurological injury. High-normal $PaCO_2$ and moderate hyperoxia resulted in increased cerebral oxygenation, but this was not associated with the extent of brain injury. In patients with AMI and vasopressor dependent hypotension, targeting a MAP between 80/85-100 mmHg was associated with smaller myocardial injury without clinically significant side effects.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a major cause of morbidity and mortality worldwide and causes millions of premature deaths every year [1]. Although the overall survival of OHCA patients is relatively low and has remained more or less stable over the years, the prognosis of witnessed OHCA with a shockable initial rhythm and presumed cardiac origin has improved significantly during the last decade. According to the latest reports in Finland, about a third of these patients were alive one year after the event, and in metropolitan areas the one-year survival rate was as high as 54% [2]. Nine out of ten survivors reached good neurological recovery and were living independent lives one year after cardiac arrest (CA) [3].

Several pre-hospital factors have probably contributed to the better prognosis of OHCA patients [4]. These include improved public awareness, increased bystander cardiopulmonary resuscitation (CPR) skills, efficient emergency medical service (EMS) systems, focus on high-quality CPR, and reduced delays from collapse to defibrillation. After return of spontaneous circulation (ROSC), most OHCA patients suffer from a systemic ischaemia-reperfusion injury, hypoxic ischaemic encephalopathy (HIE), and myocardial dysfunction. Together, these pathophysiological processes form the post-cardiac-arrest syndrome, causing significant mortality and morbidity in resuscitated patients [5]. In contrast to the pre-hospital phase, efficient post-ROSC interventions are scarce, and targeted temperature management (TTM) is the only therapy that has been proved to improve outcomes and implemented in clinical practice [6-8]. Inhaled xenon seems to attenuate myocardial injury and white matter damage in the brain, but its effect on outcome remains undefined [9,10]. In OHCA patients with acute coronary occlusion, early reperfusion with percutaneous coronary intervention (PCI) has been suggested to be beneficial but the evidence remains inconclusive [11].

Brain injury caused by HIE is the major cause of death and disability after successful resuscitation from OHCA [12]. Initially, the developing neurological damage is thought to be related to a global ischaemia-reperfusion injury and an increase in reactive oxygen species (ROS), which may increase the oxidative damage to the brain [13]. Subsequently, this is followed by cerebral hypoperfusion, possibly caused by increased vasoconstriction during the first 72 h of post-resuscitation care, further aggravating the developing brain injury [14]. Arterial carbon dioxide tension ($PaCO_2$), arterial oxygen tension (PaO_2), and arterial pressure all affect cerebral oxygen delivery when the autoregulation of cerebral blood flow (CBF) is disturbed because of HIE. In unconscious, mechanically ventilated patients, $PaCO_2$, PaO_2, and blood pressure can be modified via ventilator settings or vasoactive drug infusions, and it is reasonable to think that by optimising their levels during the first days after

resuscitation the cerebral hypoperfusion could be prevented and the developing brain damage minimised. However, due to the lack of high-quality data, the optimal targets of $PaCO_2$, PaO_2 and blood pressure remain unknown [15].

Review of the literature

Out-of-hospital cardiac arrest

The exact incidence of OHCA is unknown. Not all cases are attended or reported by EMS, and even the definition of OHCA can vary regionally. Globally, the incidence of EMS-treated OHCA in adult population has been estimated to be approximately 62 per 100 000 person-years [1]. Less than 10% of these patients survive to hospital discharge, making OHCA a leading cause of mortality worldwide. Geographical variation in the incidence of OHCA is extensive, mostly because of different cardiovascular risk profiles between populations and variation in identifying the cases. The regional disparity in outcome is even more pronounced, with a tenfold difference in survival between some areas. This reflects not only the hugely different population density and response delays between different regions, but also the variation in public awareness, efficiency of EMS systems, and quality of hospital care [16].

The most common cause of OHCA is ischaemic heart disease, typically presenting as a sudden plaque rupture in one of the coronary arteries, leading to thrombus formation, coronary occlusion, and abrupt myocardial ischaemia [17,18]. Other cardiac causes of OHCA include cardiomyopathy, valvular heart disease, and congenital anatomic and electrical abnormalities, all of which are potential causes of lethal arrhythmias. In OHCA patients with cardiac aetiology, the initial rhythm is usually ventricular fibrillation (VF) [19]. Without prompt CPR and defibrillation, VF slowly deteriorates to pulseless electrical activity (PEA) and eventually asystole, reducing the chance for survival by approximately 10% per minute [20]. The most frequent non-cardiac aetiologies of OHCA are trauma, non-traumatic bleeding, pulmonary embolism, asphyxia, respiratory failure and hypoxia, metabolic disturbances, and intoxication [19]. In these conditions the pathophysiological processes behind the cardiac arrest (CA) vary widely, and the typical initial rhythm is pulseless electrical activity (PEA) or asystole.

Most of OHCA patients with attempted resuscitation by EMS have a cardiac cause for the arrest. However, the proportion of VF as initial rhythm has declined over the last decades [1], and according to the latest reports in Finland, approximately one third of the OHCA patients with attempted resuscitation had a shockable initial rhythm [2]. At the same time, the incidence of PEA has been increasing [21]. Improvements in the primary and secondary prevention of coronary artery disease and increased use of implantable cardioverter defibrillators have probably reduced the risk for OHCA with a cardiac aetiology. Because the number of elderly people in most western societies is increasing, the overall incidence of OHCA has not declined and the proportion of non-shockable initial rhytms is more pronounced than before.

Known baseline factors affecting outcome after OHCA include patient age, comorbidities, socioeconomic status, the cause of CA, and presenting initial rhythm [16]. Bystander CPR has been found to be the most important intervention associated with survival in OHCA patients [4]. Other factors with a strong association with outcome include the delays to CPR and defibrillation, the time without compressions during advanced life support (ALS), and the delay to ROSC. The chain of survival is a concept used to describe the necessary elements needed for successful resuscitation [20]. It consists of early recognition of CA and call for help, rapid activation of the EMS system, prompt initiation of bystander CPR, early defibrillation, effective ALS, and coordinated post-resuscitation care. Seamless cooperation of the public, emergency dispatchers, paramedics, EMS physicians, and hospital staff is required for the resuscitation attempt to be successful and the patient to survive.

After ROSC, many patients remain unconscious for several days after the CA. Accurate prognostication during this phase is essential to avoid falsely pessimistic prognosis in the individuals who have a chance to recover and, on the other hand, to avoid unnecessarily prolonged intensive care in futile situations. Multimodal prognostication strategy combining neurological examination, radiological imaging, neurophysiological assessment, and biomarkers is recommended by international guidelines [15].

Carbon dioxide and HIE

Carbon dioxide (CO_2) is produced in all aerobic organisms as a waste product of cellular respiration [22]. In blood, CO_2 reacts with water and forms carbonic acid (H_2CO_3), which in turn partly dissociates into bicarbonate (HCO_3^-) and H^+, increasing the acidity and lowering the pH of the blood. Changes in CO_2 and H^+ concentrations are sensed by chemosensitive receptors in the carotid body and in the brain, leading to some important physiologic changes affecting the respiratory, cardiovascular and central nervous systems of the body. In addition to its crucial role in controlling lung ventilation, $PaCO_2$ is a major determinant of CBF [23]. Hypercapnia increases CBF by increasing arterial pressure and by causing vasodilation in the arterioles and precapillary sphincters in the brain. Elevated $PaCO_2$ increases the H^+ concentration in endothelial cells, leading to activation of voltage-gated K^+ channels and hyperpolarisation of the cell. This reduces intracellular calcium concentration and causes smooth muscle relaxation, resulting in vasodilation of the vessel. In patients resuscitated from CA, the normal autoregulation of CBF is often disturbed due to the developing brain injury [24], but the reactivity to changes in $PaCO_2$ remains functional even when the autoregulation of CBF is impaired [14].

In addition to its effect on CBF, CO_2 seems to be neuroprotective by several mechanisms. Increasing $PaCO_2$ shifts the Hb-O_2 dissociation curve to the right, increasing the release of oxygen to the tissues and thus, theoretically, facilitating the oxygen delivery to the brain [25]. Hypercapnia may activate the hypothalamic-pituitary-adrenal axis and alter the secretion and function of various brain neurotransmitters,

leading to antioxidant and anti-inflammatory effects [26]. Moreover, CO_2 has been shown to have anticonvulsant properties, and inhaling 5% CO_2 has had a potent effect on cortical epileptic activity both in animal models and human epilepsy patients [27]. In experimental models in rats, moderate hypercapnia ($PaCO_2$ 8.0–13.3 kPa) has been associated with better neurological outcome and less severe histological brain damage as compared with normocapnia or severe hypercapnia after global cerebral ischemia [28]. In contrast, in a recent study with pigs, mild hypercapnia (6.0-6.7 kPa) during the first 4 h after ROSC was associated with higher MAP when compared to normocapnia, but there was no difference in markers of neurological or cardiac injury or outcome [29]. However, in histological assessment, mild hypercapnia was associated with a decrease in neuronal degeneration in the frontal cortex.

Besides the potential benefits, there are some major risks related to elevated $PaCO_2$ levels in comatose CA patients. First, hypercapnia increases CBF and cerebral blood volume [22], potentially leading to further increase of intracranial pressure (ICP) in patients already suffering from cerebral oedema caused by HIE. Second, hypoventilation and hypercapnia aggravate acidosis, which is in turn associated with poor neurological outcome after CA [30]. Hypercapnic acidosis may cause vasoconstriction of the pulmonary blood vessels, leading to right ventricular systolic overload. Third, acute hypercapnia impairs myocardial function [22]. In patients with severe acute respiratory distress syndrome (ARDS), acidosis and hypercapnia have been associated with impaired right ventricular function and hemodynamic instability [31].

The results of several human studies regarding different $PaCO_2$ levels in resuscitated patients have supported the idea that hypercapnia could be beneficial after CA (Table 1). In a large Australian cohort study, 16 542 CA patients were classified to hypocapnia, normocapnia or hypercapnia according to a single arterial blood gas (ABG) analysis during the first 24 h of ICU care. As compared with normocapnia, hypocapnia was associated with poor outcome but hypercapnia was associated with comparable mortality with a higher chance of being discharged home among survivors [32]. In a prospective observational study of 409 Finnish OHCA patients, hypercapnia was associated with good neurological outcome at 12 months [33]. Before the present study, only one randomised trial comparing different $PaCO_2$ levels in CA patients has been completed. In this study, targeting mild hypercapnia (6.7– 7.3 kPa) instead of normocapnia in 83 CA patients during the first 24 h of intensive care unit (ICU) care attenuated the increase of neuron-specific enolase (NSE) and S100 calcium-binding protein B (S100B) concentrations over time, supporting the possible protective effect of CO_2 against neurological injury [34]. Moreover, no adverse effects related to mild hypercapnia were reported. Recently, in another prospective cohort study of 280 CA patients, the probability for good neurological outcome at hospital discharge increased as $PaCO_2$ during the first six hours after ROSC increased up to 9.1 kPa [35].

At the same time, however, many studies have reported contradicting results, suggesting that hypercapnia is detrimental during the post-resuscitation phase. In two consecutive prospective cohort studies carried out at the same university hospital in the United States, the $PaCO_2$ results of 75 and 193 CA patients during the first

Table 1 Previous studies investigating the association between $PaCO_2$ and outcome after cardiac arrest

Study	N:o of patients		Study design	Main findings
Moon 2007	44	IHCA	Prospective cohort study, single centre	No difference in $PaCO_2$ between survivors and non-survivors
Roberts 2013	193	OHCA / IHCA	Prospective cohort study, single centre	Hypercapnia was independently associated with poor neurological outcome at hospital discharge
Schneider 2013	16 542	OHCA / IHCA	Retrospective cohort study, multicentre	Hypercapnia was associated with similar hospital mortality but higher rate of discharge home among survivors as compared with normocapnia
Lee 2014	213	OHCA / IHCA	Retrospective cohort study, single centre	Hypercapnia was not associated with increased hospital mortality as compared with normocapnia
Roberts 2014	75	OHCA / IHCA	Prospective cohort study, single centre	Normocapnia was associated with good neurological outcome at hospital discharge as compared with hypocapnia or hypercapnia
Vaahersalo 2014	409	OHCA	Prospective cohort study, multicentre	Hypercapnia was associated with good 12-month outcome as compared with normocapnia
Eastwood 2015	120	OHCA / IHCA	Retrospective cohort study, single centre	No difference in $PaCO_2$ between survivors and non-survivors
Helmerhorst 2015	5 258	OHCA	Retrospective cohort study, multicentre	$PaCO_2$ had an independent U-shaped relationship with hospital mortality
Wang 2015	550	IHCA	Retrospective cohort study, single centre	Increasing $PaCO_2$ was inversely associated with good neurological outcome
Eastwood 2016	86	OHCA / IHCA	Randomised controlled trial, multicentre	Serum NSE concentration during the first 72 h was significantly lower in patients allocated to mild hypercapnia as compared with normocapnia
McKenzie 2017	23 434	OHCA / IHCA	Systematic review and meta-analysis	Normocapnia was associated with increased hospital survival and good neurological outcome as compared with hypercapnia
Tolins 2017	114	OHCA	Retrospective cohort study, multicentre	Normocarbia at hospital admission was associated with good neurological outcome as compared with dyscarbia
Wang 2017	9 186	OHCA	Prospective cohort study, multicentre	Hypercapnia was associated with increased hospital mortality as compared with normocapnia
Ebner 2018	869	OHCA	Post hoc analysis of a randomized tiral, multicentre	No significant association between $PaCO_2$ and neurological outcome at 6 months was detected
Pitcher 2018	222	OHCA / IHCA	Retrospective cohort study, single centre	Hypercapnia or hypocapnia during the first 24 h after hospital admission were not associated with neurological outcome at hospital discharge
Kilgannon 2019	280	OHCA / IHCA	Prospective cohort study, multicentre	Probability for good neurological outcome increased as $PaCO_2$ increased up to 9.1 kPa

Abbreviations: $PaCO_2$, arterial carbon dioxide tension; IHCA, in-hospital cardiac arrest; and OHCA, out-of-hospital cardiac arrest.

24 h after hospital admission were analysed. The investigators concluded that in both studies, hypercapnia was associated with poor neurological outcome at hospital discharge when compared with normocapnia [36,37]. A Dutch retrospective cohort study of 5 258 mechanically ventilated CA patients found that $PaCO_2$ during the first 24 h after ICU admission had an independent U-shaped relationship with hospital mortality and both hypocapnia and hypercapnia were associated with poor outcome [38]. Another retrospective cohort study of 550 in-hospital cardiac arrest (IHCA) patients from Taiwan reported similar results, concluding that increasing values of the first obtained $PaCO_2$ after ROSC were associated with poor neurological outcome [39]. A systematic review and meta-analysis of 9 observational studies executed between 1985 and 2015 stated that both hypocapnia and hypercapnia seem to be detrimental when compared with normocapnia after CA [40]. More recently, two more observational studies of 114 and 9 186 OHCA patients, respectively, have reported results favouring normocapnia over hypercapnia [41,42]. In addition, the results of several studies have been neutral, and no association between hypercapnia and mortality or neurological outcome has been found [43-47].

Oxygen exposure in resuscitated patients

Adequate oxygen delivery to the tissues is vital during acute conditions such as CA [48]. The brain is particularly susceptible to even short interruptions of oxygen supply. During CPR, efficient airway management and ventilation of the lungs are essential to achieve ROSC and to prevent secondary hypoxic damage to the brain. For this purpose, current guidelines recommend aiming for maximal fraction of inspired oxygen (FiO_2) during resuscitation [49]. Immediately after ROSC the situation becomes more complicated, however, and according to the current recommendations FiO_2 should be titrated to aim SpO_2 94-98% to avoid the potential detrimental effects of hyperoxia [15].

Inadequately high PaO_2 after global ischaemia and reperfusion may increase the production of ROS [50]. They are highly reactive and unstable molecules that are known to cause lipid peroxidation, protein oxidation, and DNA damage [13]. The increased production of ROS can exacerbate the neurological injury after resuscitation, and experimental studies in animals have shown that exposure to very high levels of PaO_2 during the early stages of reperfusion after CA may increase histological damage to neurons and lead to poor neurological outcome [51]. In addition, hyperoxia decreases cardiac output (CO) and capillary perfusion, which may further account for the possible detrimental effects of hyperoxia after CA [13].

The effects of hyperoxia after resuscitation in humans were first investigated in a small randomised trial of 28 OHCA patients who were ventilated with either 30% or 100% FiO_2 immediately after ROSC (Table 2). The authors observed a statistically significant increase in NSE within a subgroup of patients exposed to 100% oxygen and not treated with TTM at 33 °C, indicating a harmful effect of extreme hyperoxia in patients without the protecting effect of hypothermia [52]. Due to its small size, this

Table 2 Previous studies investigating the association between PaO_2 and outcome after cardiac arrest

Study	N:o of patients		Study design	Main findings
Kuisma 2006	32	OHCA	Randomised trial, single centre	FiO_2 100% was associated with increased NSE at 24 h in patients not treated with TH when compared with FiO_2 30%
Kilgannon 2010	6 326	OHCA / IHCA	Retrospective cohort study, multicentre	PaO_2 > 40 kPa in the first ABG analysis in ICU was associated with increased in-hospital mortality
Kilgannon 2011	4 459	OHCA / IHCA	Retrospective cohort study, multicentre	Increasing PaO_2 during the first 24 h after ICU admission was associated with increased in-hospital mortality and poor functional outcome
Bellomo 2011	12 108	OHCA / IHCA	Retrospective cohort study, multicentre	No consistent association between PaO_2 and in-hospital mortality
Janz 2012	170	OHCA / IHCA	Prospective cohort study, single centre	Higher PaO_2 during the first 24 h after ICU admission was associated with increased in-hospital mortality
Ihle 2013	584	OHCA	Retrospective cohort study, multicentre	PaO_2 > 40 kPa was not associated with increased in-hospital mortality in OHCA patients with VF as the initial rhythm
Nelskylä 2013	119	OHCA / IHCA	Prospective cohort study, single centre	PaO_2 > 40 kPa was not associated with increased 30-day mortality
Lee 2014	213	OHCA / IHCA	Retrospective cohort study, single centre	PaO_2 was not independently associated with increased hospital mortality
Oh 2014	792	IHCA	Retrospective cohort study, multicentre	PaO_2 during the first 2 hours after ROSC was not associated with in-hospital mortality or neurological outcome
Vaahersalo 2014	409	OHCA	Prospective cohort study, multicentre	No association between hyperoxia exposure and neurological outcome at 12 months
Wang 2014	49 951	OHCA / IHCA	Systematic review and meta-analysis	PaO_2 > 40 kPa was associated with increased in-hospital mortality
Elmer 2015	184	OHCA / IHCA	Prospective cohort study, single centre	PaO_2 > 40 kPa was associated with increased in-hospital mortality, but PaO_2 14-40 kPa was associated with lower SOFA score at 24 h
Helmerhorst 2015	5 258	OHCA	Retrospective cohort study, multicentre	Hyperoxia was not independently associated with increased in-hospital mortality as compared with normoxia
Helmerhorst 2015	49 389 [a]	OHCA / IHCA	Systematic review and meta-analysis	Hyperoxia was associated with poor hospital outcome
von Auenmuller 2017	170	OHCA	Retrospective cohort study, single centre	PaO_2 during the first hour after hospital admission was not associated with increased 5-day mortality
Johnson 2017	544	OHCA	Retrospective cohort study, multicentre	PaO_2 during the first 48 h after hospital admission was not associated with neurological outcome at hospital discharge, but PaO_2 at 12 h was associated with increased in-hospital mortality

Table 2 Continued

Study	N:o of patients		Study design	Main findings
Wang 2017	9 186	OHCA	Prospective cohort study, multicentre	PaO_2 > 40 kPa during the first 24 h after hospital admission was associated with increased in-hospital mortality
Patel 2018	40 573	OHCA / IHCA	Systematic review and meta-analysis	Post-arrest hyperoxia was associated with increased mortality
Roberts 2018	280	OHCA / IHCA	Prospective cohort study, multicentre	PaO_2 > 40 kPa was associated with poor neurological outcome at hospital discharge
Ebner 2019	869	OHCA	Post hoc analysis of a randomised trial	No association between hyperoxia exposure and neurological outcome at 6 months

Abbreviations: PaO_2, arterial oxygen tension; OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; FiO_2, fraction of inspired oxygen; NSE, neuron-specific enolase; TH, therapeutic hypothermia; ABG; arterial blood gas; ICU, intensive care unit; VF, ventricular fibrillation; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment.

[a] The total number of patients analysed includes patients with cardiac arrest, traumatic brain injury, stroke, subarachnoid haemorrhage and any mechanical ventilation

study was not powered to detect differences in neurological recovery or mortality between the groups. Later, two large observational studies using pre-defined limits for hypoxia (PaO_2 < 8 kPa), normoxia (PaO_2 8-40 kPa), and hyperoxia (> 40 kPa) reported conflicting results on the effects of hyperoxia during post-resuscitation care. In the first one, a multicentre cohort study of 6 326 CA patients, hyperoxia in the first ABG analysis obtained in the ICU was independently associated with in-hospital mortality when compared with normoxia or hypoxia [53]. In further analysis of the same database, the investigators found a linear relationship between increasing PaO_2 values over 40 kPa and risk of in-hospital death [54]. In the second study analysing a multicentre cohort of 12 108 patients, both hyperoxia and hypoxia during the first 24 h of ICU care were associated with increased mortality in comparison to normoxia. However, when illness severity score was taken into account, this association was markedly reduced, and the authors concluded that hyperoxia did not have a clear and consistent independent relationship with mortality [55].

Later, several observational studies have found a positive association between severe hyperoxia (PaO_2 > 40 kPa) exposure during early intensive care after CA and increased mortality or poor neurological outcome [42,56-58]. On the other hand, numerous studies have concluded that they were unable to demonstrate that such an association exists [33,38,44,59-63]. Three systematic reviews and meta-analyses summing up the results of the observational studies investigating the relationship between hyperoxia and outcomes in CA patients have been published between 2014 and 2018 [64-66]. All of them concluded that severe hyperoxia appeared to be associated with increased in-hospital mortality. Because of significant heterogeneity in the methodology and definitions between the included studies, the authors of all reviews stated that the results should be interpreted cautiously and that more research is needed. In a recent randomised trial comparing conservative (target SpO_2 91-97%) versus usual

(target SpO_2 ≥ 91%) oxygen therapy in 965 mechanically ventilated ICU patients, no difference in ventilator-free days or mortality was found between the groups [67]. However, only a minority (17%) of the included participants in this study were resuscitated CA patients suffering from HIE.

Based on the literature published so far, it seems that severe hyperoxia is probably detrimental after CA, but the effect of moderate hyperoxia (PaO_2 15-40 kPa) remains unclear. Interestingly, in a prospective observational study of 409 Finnish OHCA patients with frequent ABG analyses during the first 24 h in ICU, the investigators were unable to detect any harm from hyperoxia exposure and suggested that the PaO_2 associated with the lowest mortality was around 20 kPa [33]. Another prospective observational study of 184 patients with repeated ABG samples over the first 24 h concluded that severe hyperoxia (PaO_2 > 40 kPa) was associated with increased in-hospital mortality, but in contrast, moderate hyperoxia was associated with improved organ function at 24 h after CA [57].

Arterial blood gas analysis

The analysis of ABGs refers to the measurement of PaO_2, $PaCO_2$, pH, and the oxygen saturation of haemoglobin in arterial blood. In critical care, the sample is usually obtained via arterial cannula and the analysis is done immediately with a point-of-care device available in many ICUs. The usual indications for ABG analysis are the diagnosis and follow-up of critical conditions that alter gas exchange or acid-base balance, and the assessment of oxygenation and ventilation in mechanically ventilated patients.

Several factors can alter the results of ABG analysis [68]. First, the sample needs to be obtained anaerobically into a gas-tight syringe in order to avoid oxygen and carbon dioxide entering or leaving the sample. Even small bubbles of air can significantly alter the PaO_2, $PaCO_2$, and pH in the blood. Second, haemolysis in the sample can affect ABG results. As the gradient of PaO_2, $PaCO_2$, and pH between plasma and red blood cells is not large, this effect is rarely clinically relevant. Third, in any whole blood sample where living cells are interacting with nutrients and oxygen, the metabolism can continue. As a result, $PaCO_2$ increases and PaO_2 and pH decrease over time. This can distort the ABG results if the sample is stored for a long time before analysis. Fortunately, this is rarely a problem in modern ICU environment because most of the time ABGs are analysed on-site immediately after obtaining the sample.

A major issue regarding ABG analyses of resuscitated patients treated with TTM is the effect of temperature on PaO_2, $PaCO_2$, and pH. As the temperature of blood decreases, the solubility of oxygen and CO_2 increase, lowering their partial pressures and changing the relationship between partial pressure and the total content of oxygen and CO_2 in the blood [68]. Moreover, because the dissociation of an acid (i.e. H_2CO_3) to the corresponding cation (HCO_3^-) and H^+ is an endothermic reaction requiring energy, cooling of the blood will shift the balance of the equilibrium

towards H_2CO_3, reducing the concentration of H^+ and increasing the pH [69]. Because the reference ranges of PaO_2, $PaCO_2$, and pH have been defined in healthy volunteers at 37°C and there is limited knowledge of their normal values in varying temperatures, the interpretation of the ABG results in hypothermic patients can be challenging.

Two different scientific models exist to analyse $PaCO_2$ and pH in different temperatures: In alpha-stat the results are interpreted at normal body temperature (37°C), whereas in pH-stat the temperature is corrected to the patient's actual temperature [70]. Because the complex effects of temperature on metabolism, circulation, and respiration are not fully understood, neither method can be stated to be correct, and the choice should be made depending on the clinical situation. From the physiological perspective, correcting pH for temperature may not seem logical because the pH of neutrality also changes with temperature. However, during therapeutic hypothermia, interpreting $PaCO_2$ values corrected to the patients' actual temperature might be more reasonable [71].

During TTM with a target temperature of 33°C, the $PaCO_2$ measured with pH-stat is approximately 10% lower than the $PaCO_2$ measured with alpha-stat [45]. This means that lower-threshold normocapnia according to alpha-stat would be interpreted as clear hypocapnia with pH-stat. At the same time, the metabolic rate of the hypothermic body is reduced, leading to lower CO_2 production in the cells and increasing the risk for unintentional hypocapnia with conventional ventilator settings. Indeed, lower-threshold normoventilation according to temperature non-corrected $PaCO_2$ has been shown to lead to lower jugular bulb oxygen saturation and increased risk of cerebral vasoconstriction and ischemia during TTM [72].

Regarding oxygen, the effects of cooling are somewhat different. In contrast with CO_2, the amount of oxygen in inspired air and in the alveoli is kept constant by adjusting the FiO_2 in mechanically ventilated patients [70]. The partial pressure of oxygen in the alveolar air equilibrates with the partial pressure of oxygen in the alveolar capillaries, keeping PaO_2 essentially constant despite the lowering temperature and the increasing solubility of oxygen in the blood. At the same time, the oxyhaemoglobin dissociation curve is shifted to the left, increasing the affinity of haemoglobin to oxygen. Moreover, the decreased metabolic rate during hypothermia reduces oxygen consumption in the cells. Altogether, this means that the total oxygen content in the blood increases with cooling temperature. Considering the dynamics of PaO_2 in hypothermic patients, the interpretation of PaO_2 level should always be made corrected to the actual temperature during TTM in order to maintain adequate oxygenation and to avoid desaturation.

Blood pressure after cardiac arrest

Hemodynamic instability and hypotension are common after CA and resuscitation. They are thought to be the result of various different mechanisms related to the global ischaemia-reperfusion injury and some other factors. First, myocardial

stunning caused by the ischaemia-reperfusion injury can lead to acute myocardial dysfunction and low CO [73]. Second, resuscitated patients suffer from a sepsis-like systemic inflammation response syndrome that leads to disturbances in the inflammatory cascade and increases the levels of various cytokines, causing systemic vasodilation and low cardiac filling pressures [74]. Third, relative adrenal axis insufficiency is common in CA patients, further aggravating the haemodynamic instability [75]. Finally, acute coronary syndrome (ACS) is the most common cause of OHCA, and many resuscitated patients suffer from myocardial ischaemia or acute myocardial infarction (AMI). This can potentially affect cardiac contractility and lead to decreased CO [76].

As a result of the developing brain injury after CA, CBF autoregulation is disturbed and right-shifted in many patients, meaning that CBF may become directly dependent on MAP [24]. In addition, hypoxia-induced cerebral swelling can increase ICP, and together with systemic hypotension this can severely compromise adequate cerebral perfusion pressure (MAP minus ICP). Thus, arterial hypotension after CA can lead to cerebral hypoperfusion and aggravate the developing brain damage. In experimental studies with animals, increasing MAP with vasoactive agents after CA has indeed been associated with better outcomes [77].

So far, many observational human studies have found an association between post-ROSC hypotension and poor outcome [78-91] (Table 3). In contrast, only one study has reported that no association between MAP and outcome was observed [92]. In a systematic review of 9 observational studies performed between 2008 and 2105, higher blood pressure level during the post-resuscitation phase was associated with improved neurological outcomes [93]. However, most of the studies included both OHCA and IHCA patients, and there was marked methodological heterogeneity between them. In addition, in most of the studies blood pressure was recorded only for a relatively short period of time (6-24 h) after ICU admission. More recently, several new studies assessing the relationship between post-ROSC hypotension and outcome specifically in OHCA patients have been published. In a post hoc analysis of the TTM trial [8], hypotension (MAP < 65 mmHg) during the first 36 h in ICU was associated with increased 30-day mortality [86]. In a prospective multicentre observational study in Finland, a total of 1.2 million blood pressure values of 412 patients measured during the first 48 h of ICU care were analysed. The authors concluded that hypotension during the first six hours was an independent predictor of poor neurologic outcome at one year, but hypotension later during the intensive care was not [87]. In another small observational study extending the blood pressure monitoring to 96 h after hospital admission, hypotension (MAP < 75 mmHg) was again associated with poor outcome[91]. Interestingly, the authors found that the effect of MAP on outcomes was attenuated with increasing age.

During intensive care, blood pressure can be regulated with fluid infusions and vasoactive agents. Based on the studies performed so far, it has been hypothesised that targeting a higher MAP during the early post-resuscitation period would improve clinical outcomes. However, no randomised trials comparing the effect of two different blood pressure levels have been conducted before. Due to the lack of

Table 3 Previous studies investigating the association between blood pressure and outcome after cardiac arrest

Study	N:o of patients		Study design	Main findings
Kilgannon 2008	102	OHCA / IHCA	Retrospective cohort study, single centre	Hypotension (SAP < 100 mmHg at least twice) within the first 6 h after ROSC was associated with higher in-hospital mortality
Trzeciak 2009	8 736	OHCA / IHCA	Retrospective cohort study, multicentre	Hypotension (SAP < 90 mmHg) within 1 h after ICU arrival was associated with higher in-hospital mortality
Kaji 2011	73	OHCA	Retrospective cohort study, single centre	Hypotension (SAP < 90 mmHg or MAP < 60 mmHg) within the first 24 after ROSC was associated with higher in-hospital mortality
Beylin 2013	168	OHCA / IHCA	Prospective cohort study, multicentre	Lower MAP during the first 24 h after ROSC was associated with increased in-hospital mortality; increasing use of vasoactive agents was associated with increased mortality and lower CPC scores
Kim 2013	4 617	IHCA	Prospective cohort study, multicentre	Lowest MAP at 24 h after ICU admission was associated with in-hospital mortality
Bray 2014	3 620	OHCA	Prospective cohort study, multicentre	Hypotension (SAP < 90 mmHg) at hospital arrival was associated with higher in-hospital mortality in patients with shockable initial rhythm
Kilgannon 2014	151	OHCA / IHCA	Prospective cohort study, single centre	Time-weighted average MAP during the first 6 h after ROSC was associated with good neurological outcome at hospital discharge
Ameloot 2015	82	OHCA / IHCA	Prospective cohort study, single centre	MAP between 76-86 mmHg during the first 24 h in ICU was associated with highest survival
Bhate 2015	13 150	OHCA / IHCA	Systematic review	Higher blood pressure post ROSC was associated with improved outcomes
Bro-Jeppesen 2015	920	OHCA	Post hoc analysis of a randomised trial	Hypotension (MAP < 65 mmHg) during the first 36 h in ICU was associated with 30-day mortality; high dose of vasopressors was an independent predictor of 30-day mortality
Young 2015	188	OHCA / IHCA	Prospective cohort study, single centre	No association between MAP during TH and neurological outcome was observed
Laurikkala 2016	412	OHCA	Prospective cohort study, multicentre	Lowest MAP within 6 h after ROSC was associated with poor neurological outcome at 1 year
Russo 2017	122	OHCA	Prospective cohort study, single centre	Higher mean MAP during the first 96 h of hospital admission was associated with increased survival but not neurological outcome
Chiu 2018	289	OHCA	Retrospective cohort study, multicentre	Time-weighted average MAP during the first 3 h after ROSC was associated with survival and good neurological outcome at hospital discharge
Roberts 2018	269	OHCA / IHCA	Prospective cohort study, multicentre	MAP > 90 mmHg during the first 6 h after ROSC was associated with increased in-hospital survival and better neurological outcome as compared with MAP 70-90 mmHg

Table 3 Continued

Study	N:o of patients		Study design	Main findings
Russo 2018	122	OHCA	Retrospective cohort study, single centre	Hypotension (MAP < 75 mmHg) during the first 96 h after ICU admission was associated with poor neurological outcome at hospital discharge
Grand 2019	657	OHCA	Post hoc analysis of a randomised trial	MAP during TTM was not associated with NSE concentrations or survival

Abbreviations: OHCA, out-of-hospital cardiac arrest; IHCA, in-hospital cardiac arrest; SAP, systolic arterial pressure; ROSC, return of spontaneous circulation; ICU, intensive care unit; MAP, mean arterial pressure; CPC, Cerebral Performance Category; TH, therapeutic hypothermia; TTM, targeted temperature management; NSE, neuron-specific enolase.

high-quality data, the optimal MAP target remains unknown and current European guidelines recommend aiming for a MAP sufficient to achieve an adequate urine output and decreasing lactate levels [15]. In addition, there are concerns regarding the potential side effects of vasoactive and inotropic agents such as noradrenaline and dobutamine, and in some of the previous studies, both low MAP and increasing use of vasoactive agents has been associated with mortality and poor neurological outcome [81,86].

Continuous direct arterial pressure measurement is the standard method of blood pressure monitoring in ICU patients. The radial artery is the most common site for cannulation, and common alternatives include the brachial artery and the femoral artery. Several factors can affect the reliability of direct blood pressure monitoring and need to be considered when interpreting the results [94]. First, under- or overdamping of the monitoring system is common. This can cause alterations in the arterial pressure waveform and thus affect the observed blood pressure values. Underdamping typically causes systolic pressure overshoot, whereas overdamping results in an abnormally blunt waveform and an underestimation of the systolic pressure level. Fortunately, in both cases the MAP usually remains relatively accurate despite significant deviations in the systolic and diastolic pressures. Minimising the length of pressure tubing, limiting the addition of valves and connections to the system, and eliminating all air bubbles from the hosing can help to alleviate the effects of under- and overdamping. Second, the monitoring system needs to be zeroed, meaning that the zero point of the pressure scale has to be established at ambient atmospheric pressure. Failure to do this before the monitoring is begun and periodically thereafter can cause bias to the blood pressure results. Third, the pressure transducer must be appropriately leveled, setting the zero-reference point relative to the patient's body. In ICU patients, the transducer is usually placed at mid-thoracic level, aligning the reference level at the position of the left atrium. Because even small deviations of the transducer level can lead to significant changes in the measured blood pressure, the correct level must be meticulously checked, especially after the patient's position is changed.

Feasibility of targeting a specific $PaCO_2$, PaO_2, and MAP level

The main purpose of mechanical ventilation in unconscious and intubated critical care patients is to maintain adequate oxygenation of the tissues and remove CO_2 from the body when the patient is unable to breathe spontaneously. Increasing the respiratory rate (RR) and/or tidal volume (TV) on the ventilator increases the minute ventilation (MV) of the lungs and CO_2 clearance from the body, decreasing $PaCO_2$ [95]. PaO_2 can be adjusted by changing FiO_2 and by maintaining adequate positive end-expiratory pressure (PEEP) that keeps the small airways open and prevents the alveoli from collapsing. Although these relationships between MV and $PaCO_2$, and PaO_2 and FiO_2 seem fairly trivial, there are several factors that can make maintaining adequate ventilation and oxygenation challenging during intensive care. First, in patients with lung injury or ARDS, aiming for normal $PaCO_2$ with positive-pressure ventilation can lead to excessive tidal volumes and airway pressures, stretching the lungs and causing iatrogenic damage [96]. Second, atelectasis of the alveoli can cause significant shunting, and lead to persistent hypoxemia that does not respond to raising FiO_2. Third, mechanical ventilation and general anaesthesia change the distribution of both air and blood flow in the lungs, increasing ventilation-perfusion mismatch and leading to derangements in both $PaCO_2$ and PaO_2 [25]. Fourth, haemodynamic instability and reduced CO can affect peripheral tissue and lung perfusion, and thus alter the $PaCO_2$ and PaO_2 levels. In addition, decreased body temperature during TTM slows down the metabolic rate of the body, leading to reduced O_2 consumption and CO_2 production in cells [97].

Despite the recommendations of keeping $PaCO_2$ and PaO_2 within the physiologic range, deviations of both of these parameters are common after CA. In a retrospective analysis of 122 OHCA patients with frequent ABG analyses during the first 48 h after hospital admission, normocapnia was maintained in only 55% of the analysed samples [98]. In a large observational study of more than 16 000 CA patients, about 20% of the patients had at least one episode of hypocapnia, and about 40% at least one episode of hypercapnia during the first 24 h from ICU admission [32]. Derangements of both $PaCO_2$ and PaO_2 were also common in an observational study of resuscitated OHCA patients in Finland [33]. In another large observational study of over 6000 CA patients, only 19% of them had normoxia in ABG analysis performed within 24 h of ICU admission [53]. Moreover, in an analysis of an Australian ICU database of more than 150 000 critically ill patients, almost half of the mechanically ventilated patients were hyperoxaemic at some point during the first 24 h in ICU [99]. Hyperoxia exposure has been shown to be more common in OHCA patients with longer delays from collapse to ROSC, and with longer delays from ROSC to ICU admission [60].

Little data on the feasibility of targeting specific levels of $PaCO_2$ and PaO_2 exist so far. A retrospective analysis of 75 CA patients concluded that the prescribed MV after ROSC had only a weak correlation with measured $PaCO_2$ soon after ROSC [37]. In a randomised controlled pilot trial comparing mild hypercapnia with normocapnia, raising $PaCO_2$ over the normal range by adjusting RR and TV was feasible,

and good separation in $PaCO_2$ between the intervention and control groups was achieved during the first 24 h from ICU admission [34]. In a before-and-after cohort study of 105 mechanically ventilated ICU patients comparing conventional versus conservative oxygen therapy, a clear difference in both FiO_2 and PaO_2 was observed between the groups [100]. Later, similar results were observed in another study with resuscitated CA patients [101].

Regarding blood pressure, the effects of noradrenaline and other vasopressors are well documented, and adjusting MAP with vasoactive infusions during general anaesthesia is part of the daily routine in a myriad of operating rooms all over the world [25]. Noradrenaline is the vasopressor of choice in shock, and the feasibility of goal-directed therapy targeting a specific MAP range with noradrenaline infusion in critical care patients has been demonstrated [102-104]. Although no studies assessing the feasibility of blood pressure control specifically in CA patients have been done so far, there is little reason to assume that adjusting the MAP after resuscitation would be substantially more difficult than in septic or cardiogenic shock patients. However, despite the recommendations of the current guidelines to use noradrenaline with or without dopamine to maintain adequate MAP after CA [15], hypotension remains common during post-resuscitation intensive care, and studies investigating the feasibility of tight blood pressure control in this patient group are needed [105].

Markers of neurological injury

Neuron-specific enolase

NSE is a cytoplasmic glycolytic enzyme found in neurons and neuroectodermal cells [106]. It is released into the cerebrospinal fluid and bloodstream after neuronal damage and impairment of the blood-brain barrier. After CA, serum concentrations of NSE during the first 24–72 h correlate with the severity of the developing brain injury and the probability of a poor outcome [107,108].

Recent research has further confirmed the value of NSE as a marker of cerebral injury after resuscitation. In a post hoc analysis of the Targeted Temperature Management trial, Stammet and colleagues analysed a total of 1823 serum samples from 686 patients and found NSE to be a strong and robust predictor of outcome in CA patients [109]. In the largest study investigating NSE as a biomarker of neurological injury after CA so far, Streitberger and colleagues analysed the blood samples of 1053 OHCA and IHCA patients [110]. In line with the previous studies, they found that elevated NSE concentration at 72 h after CA was a strong indicator of poor outcome. In a recent post hoc analysis of the FINNRESUSCI study, Wihersaari and colleagues analysed the blood samples of 249 OHCA patients and found that the ability of NSE to predict outcome was dependent on both the patients' age and the delay to ROSC [111]. They concluded that NSE at 48 h after CA had an excellent predictive value in young patients, but in older patients it was remarkably poor. Moreover, the longer the time from collapse to ROSC, the better the ability of NSE was to predict

outcome.

Although NSE is a highly specific marker of neuronal damage, it has some major pitfalls. First, no consistently reliable cut-off values for poor outcome have been established in the different studies [112]. As such, NSE can be used only as part of the multimodal prognostication, and clinical decisions should never be based solely on NSE results. Serial measurements are probably useful because an increase of NSE between any two time points during the first 72 after CA is strongly associated with poor outcome. Second, in addition to neurons, NSE is also produced in peripheral neuroendocrine cells. NSE serum concentration may increase considerably in case of malignant proliferation of neuroendocrine cells, and it is used as a biomarker in the diagnosis, prognosis, and follow-up of malignant neuroendocrine neoplasms, most notably small cell lung cancer [113]. Very high NSE concentrations due to a neuroendocrine tumour have been described in patients with excellent neurological recovery after CA [110]. Third, substantial amounts of NSE is found in erythrocytes, and even mild haemolysis can significantly increase its concentration in the blood [114]. Moreover, there is significant variation in the measured NSE concentrations between different assays and laboratories [115]. Whether fresh or frozen samples are analysed can also affect the results.

Despite its shortcomings, NSE is the most widely available and best documented surrogate marker of brain injury after CA. It is easy to use, and the concentrations are not likely to be affected by sedation or other medications. As such, it has an established role in the routine multimodal prognostication of CA patients [116], and its use is recommended by the current guidelines [15].

S100 calcium-binding protein B

S100B is a cytoplasmic protein found primarily in astroglial cells [117]. Similarly to NSE, it is released into the bloodstream in case of brain injury, and its serum concentration during the first days after CA has been shown to have high specificity in predicting poor neurological outcome in resuscitated patients [118]. Because the evidence of S100B in the neuroprognostication of CA patients is less extensive compared to NSE, it has been recommended as a secondary marker of neurological injury during post-resuscitation care [15]. In addition to CA, S100B has been used as a marker of traumatic brain injury and blood-brain barrier permeability. Moreover, S100B is expressed in melanocytes and chondrocytes, making it a useful marker in malignant melanoma and some other neoplasms and occasionally complicating the interpretation of high concentrations in the context of CA prognostication.

Cardiac troponin T

The troponin complex is a protein cluster found in skeletal muscle and cardiac muscle cells [119]. It consists of three distinct polypeptides: troponin C, troponin T, and troponin I. The troponin complex forms a part of the contractile apparatus

of the muscle cell and thus has a pivotal role in muscle contraction. Most of the troponins are bound to the actin filaments in the sarcomeres and bind to myosin when the sarcomere contracts. In addition, small amounts of troponins exist in the cytoplasm of the muscle cell. While troponin C in cardiac muscle is identical to the troponin C in skeletal muscle, troponins I and T in the heart are cardiac specific. When cardiomyocytes are irreversibly damaged, the troponins leak into the bloodstream and their concentrations in the blood reflect the extent of myocardial cell necrosis. Detection of a rise in cardiac troponin level in a blood sample forms the foundation of current diagnostics of AMI [120].

In patients with AMI, the cardiac troponin T (TnT) concentration in plasma rises sharply and peak level is reached between 4 to 12 h after coronary occlusion. In previous studies, single time-point assessments of cardiac troponin levels, as well as the area under the 72-hour TnT curve, have correlated strongly with infarct size assessed with accurate imaging methods such as single-photon emission computed tomography (SPECT) or MRI [121]. In addition, the troponin measurements at 48 and 72 h have predicted patient outcome and left-ventricular ejection fraction after AMI [122].

The introduction of more sensitive troponin assays during the past years has further enhanced the diagnostic accuracy of ACS [119]. At the same time, the pitfalls of troponin diagnostics have been highlighted. In patients with impaired renal function, cardiac troponin levels are often chronically elevated, compromising their diagnostic performance in case of an ACS [123]. Serial troponin measurements and looking for temporal changes can be helpful in this patient group [124]. In OHCA patients, TnT levels are elevated regardless of the aetiology of the arrest, probably due to ventricular arrhythmias and direct myocardial damage during the mechanical chest compressions of CPR [125]. The TnT level has been independently associated with mortality and multi-organ failure after CA [126].

Near-infrared spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive technique to assess tissue oxygenation. It is based on reflectance spectroscopy of the near-infrared spectrum of light (wavelengths 700-1100 nm). Measuring the absorption of light in the tissue and using the principles of the Beer-Lambert law, the ratio of oxygenated haemoglobin (Hb) to total Hb and thus the regional oxygen saturation (rSO_2) in the tissue can be estimated [127]. As light in the near-infrared range penetrates biological tissues several centimetres, by placing the NIRS sensors on the forehead, the rSO_2 in the frontal cortex of the brain can be assessed. The changes in frontal rSO_2 are considered to reflect changes in the relationship between oxygen delivery and consumption in the brain [128].

Several issues limit the reliability of NIRS as an indicator of cerebral oxygenation. First, the infrared light emitted from frontal NIRS transmitter has to penetrate the skin, the skull, and the meninges before reaching the cerebral tissue. Thus, the

frontal rSO_2 reflects the mean oxygen saturation of not only the brain, but also of various other extracerebral tissues [127]. Using two separate receivers, one closer to the transmitter and the other more far apart, can help to distinguish between superficial extracerebral and deeper brain tissue saturation. Second, the effects of global ischaemia and low CBF are not evenly distributed in the brain, and oxygenation can vary significantly between different areas [129]. Importantly, some of the regions more vulnerable to ischaemia, such as the hippocampus, thalamus and cerebellum, are too deeply situated for infrared light to reach them. Therefore, these areas can suffer from hypoxia even when the oxygenation of the frontal cortex seems adequate. On the other hand, haemorrhage or local ischaemia in the frontal part of the brain can result in low frontal rSO_2 even if the oxygenation in other regions is not disturbed. Third, because of large differences in frontal rSO_2 between individuals, no universally accepted reference range for "normal" cerebral oxygenation exists [128]. Instead, 10-20% deviation from the baseline rSO_2 has been suggested to be indicative of cerebral hypoxia.

Despite its limitations, the use of NIRS monitoring to optimise cerebral oxygenation during surgery and anaesthesia seems to be associated with improved neurologic outcomes in a wide variety of surgical procedures [130]. In CA patients the situation becomes more complicated because the baseline frontal rSO_2 and the optimal target level are unknown. However, according to a recent review summing up the results of 26 different studies, higher frontal rSO_2 during on-going CPR was consistently associated with increased probability of ROSC [131]. The authors concluded that monitoring frontal rSO_2 during CA could be more helpful in terminating futile resuscitation attempts than in predicting favourable outcome.

So far, there are a limited number of studies assessing the role of NIRS during post-resuscitation care and prognostication, and the results are somewhat controversial. In a small observational study of 28 OHCA patients treated with TH, the induction of hypothermia decreased the frontal rSO_2 in all patients, but the decrease was greater in patients with poor outcome [132]. In a small feasibility study including 21 patients resuscitated from IHCA or OHCA, the median frontal rSO_2 during the first 24 h of ICU care was significantly higher in patients surviving to hospital discharge when compared to non-survivors [133]. Another study including 60 IHCA/OHCA patients concluded that patients with good neurological outcome (Cerebral Performance Category [CPC] 1-2) at six months had significantly higher median frontal rSO_2 levels during the 40-hour NIRS measurement [134]. In a Japanese study, frontal rSO_2 was measured from 672 OHCA patients at hospital arrival and those with good neurological outcome at 90 days had significantly higher rSO_2 values [135]. However, only 52 patients (8%) had a sustained ROSC at the time of the rSO_2 measurement, and the rest had still on-going CPR. The vast majority of the patients (72%) were pronounced dead in the emergency department.

Interestingly, the authors of a prospective observational study of 43 OHCA patients treated with TTM reported that the mean rSO_2 during the first 48 h of ICU care was not statistically different between patients with good and poor outcome ($62\% \pm 6$ vs. $58\% \pm 9$, respectively, $p = 0.13$) [136]. In another larger cohort of 107

OHCA patients also treated with TTM, the mean frontal rSO_2 over 48 h was significantly higher in patients with good 6-month neurological outcome when compared with those with poor outcome (68% ± 4 vs. 66% ± 5, respectively, $p = 0.035$), but the absolute difference in rSO_2 was so small that it is unlikely to have any clinical relevance [137].

Electroencephalography in resuscitated patients

Electroencephalography (EEG) is a standard investigation and an important part of the multi-modal prognostication in comatose CA patients. [116]. However, its value in outcome prediction has been limited because of a wide variety of different classification systems used, significant inter-rater variability in the interpretation of the findings, and the confounding effects of sedative drugs commonly administered in ICU. Thus, the current guidelines recommend the use of EEG only together with other methods of prognostication [15].

Despite of these limitations, using standardized interpretation, specific EEG patterns have been shown to predict neurological outcome in CA patients very accurately. In a post hoc analysis of the TTM study, the investigators analysed the EEGs of 103 patients still comatose at 72 h after CA using a standardized terminology proposed by the American Clinical Neurophysiology Society [138]. They found that highly malignant EEG patterns (burst-suppression or suppressed background with or without continuous periodic discharges) predicted poor neurological outcome at 6 months with 100% specificity and 50% sensitivity [139]. Conversely, a benign EEG was highly predictive of a good functional outcome. In another prospective cohort study, continuous EEG was recorded for at least 72 h in 388 comatose CA patients and an unfavourable EEG pattern (isoelectric, low-voltage, or burst-suppression with identical bursts) at 24 h was invariably associated with poor neurologic outcome at 6 months [140]. In a recent prospective multicentre prognostication study of 346 CA patients, malignant EEG (isoelectric or burst-suppression) predicted poor outcome again with 100% specificity [141]. In addition to its value in outcome prediction, continuous EEG monitoring can be used to detect non-convulsive seizures that can potentially cause secondary brain damage in patients with HIE.

Rationale for the current study

A pilot study is a small-scale, preliminary study that is used to test the methods and procedures that the investigators are planning to use later on a larger scale. The main purpose of a pilot study is to assess the practical and logistical aspects of a future full-scale trial and test whether the full study would be feasible or not [142]. In this way, patient recruitment, the randomisation process, and the feasibility of the interventions can be assessed before investing time and resources in a larger trial. Another benefit of pilot studies is that they can provide preliminary data regarding

the effects and safety of the studied interventions, and help to generate new hypotheses. For example, investigating the effects of different interventions on biomarkers or other non-clinical outcomes in a smaller sample of patients can give a signal of benefit or harm that can be further tested in a full-scale trial.

In critical care, there are several examples of successful pilot trials conducted before proceeding to a full-scale study [143]. However, pilot studies should not be used without awareness of the potential pitfalls. Most of the risks are mainly related to the small sample size. Because of this, pilot studies are rarely powered to detect differences in the efficacy of the studied interventions, and their results regarding clinical endpoints may be overinterpreted [144]. As a consequence, conducting a full-scale trial can be abandoned altogether, and important research questions may remain unanswered. Similarly, pilot trials are usually not powered to confidently detect adverse effects related to the interventions, and for this reason, they should not be used for the safety assessment of a full study. In addition, because of the small sample size, the results of a pilot trial should be used cautiously in the sample size calculations for a full-scale trial [145]. When interpreting the feasibility results of a pilot study, it should be kept in mind that the results obtained in a small number of highly motivated centres might be misleading, and the same procedures in different critical care environments in multiple different countries can turn out to be much more challenging.

As mentioned before, $PaCO_2$, PaO_2, and MAP are modifiable factors that affect cerebral oxygen delivery when the autoregulation of CBF is disturbed in resuscitated patients suffering from HIE. The results of previous studies suggest that optimising the levels of $PaCO_2$, PaO_2, and MAP during the first days after resuscitation could mitigate the developing brain injury and have an effect on patient outcome. If proven safe and effective, this kind of intervention would be easy to implement, and the additional costs compared to current practice would be minimal. Because of the lack of high-quality data, however, the definitive targets remain undefined [15]. With the current pilot study, we wanted to fill this gap in the knowledge in two ways: First, we wanted to test if tight control of $PaCO_2$, PaO_2 and MAP during post-resuscitation care is feasible in a relatively small sample of patients before planning a full-scale trial. Second, we wanted to obtain data on the effects of these different levels of $PaCO_2$, PaO_2 and MAP on surrogate markers of cerebral and myocardial injury, cerebral oxygenation, and epileptic activity to decide whether a larger trial with similar interventions would be justified, and to identify the interventions that would most likely have an effect on mortality and neurological outcome.

Aim of the study

The aim of the current study was

1. To determine the feasibility of targeting low-normal or high-normal $PaCO_2$, normoxia or moderate hyperoxia, and low-normal or high-normal MAP in comatose patients after OHCA and successful resuscitation (I-III).
2. To assess the effect of low-normal vs. high-normal $PaCO_2$, normoxia vs. moderate hyperoxia, and low-normal vs. high-normal MAP on markers of neurological and myocardial injury, cerebral oxygenation, and epileptic activity in comatose patients after OHCA and successful resuscitation (II, III, and V).
3. To investigate the association between cerebral oxygenation and the extent of cerebral injury as assessed with markers of brain injury and neurological outcome after OHCA and successful resuscitation (IV).

Materials and methods

Study setting and design

Targeting low- or high-normal Carbon dioxide, Oxygen, and Mean arterial pressure After Cardiac Arrest and REsuscitation (COMACARE) was a prospective, multi-centre, randomised trial with 2^3 factorial design. A total of 123 unconscious, mechanically ventilated patients successfully resuscitated after OHCA were randomly assigned to targeting low-normal or high-normal $PaCO_2$, normal or moderately elevated PaO_2, and low-normal or high-normal MAP for the first 36 h in the ICU. Accordingly, each patient was randomised into one of eight groups, each group having a different combination of targets for $PaCO_2$, PaO_2 and MAP.

A summary of the study characteristics is presented in Table 4. The first publication (I) was the protocol for the COMACARE trial including a detailed plan for data collection, statistical analyses, and definition of the primary and secondary outcomes. The main results of the COMACARE trial regarding the pre-defined primary and secondary outcomes were reported in studies II and III. Study IV was a post hoc analysis of the COMACARE trial assessing the associations between cerebral oxygenation, NSE, and neurological outcome. Study V was a pooled analysis of the COMACARE and the Neuroprotect [146] trials analysing the effect of MAP on developing myocardial damage after OHCA and AMI.

Table 4 Study characteristics

Study #	Study design	N:o of patients	Main objectives
I	Protocol for a randomised trial	N/A	To define the methods and outcomes for a randomised clinical trial (studies II-III)
II	Prospective randomised trial	120	To determine the feasibility of targeting low–normal or high–normal MAP after OHCA and its effect on markers of neurological injury
III	Prospective randomised trial	120	To determine the feasibility of targeting low–normal or high–normal $PaCO_2$ and normoxia or moderate hyperoxia after OHCA and their effect on markers of neurological injury
IV	Post hoc analysis of a randomised trial	118	To investigate the association of cerebral oxygenation during early intensive care with markers of neurological injury and neurological outcome after OHCA
V	Post hoc analysis of two randomised trials	120	To investigate the association of MAP with the extent of myocardial injury in patients with AMI and vasopressor dependent hypotension after OHCA

Abbreviations: MAP, mean arterial pressure; OHCA, out-of-hospital cardiac arrest; $PaCO_2$, arterial carbon dioxide tension; and AMI, acute myocardial infarction.

Participants and consent

The eligible participants in the COMACARE trial included adult patients resuscitated from witnessed OHCA with a shockable initial rhythm (VF or pulseless VT). In addition, all of the inclusion criteria and none of the exclusion criteria had to be met (Table 5). 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 by a study nurse or ICU staff.

Because of the nature of the trial, the patients' unconscious state, and the need for a timely intervention, obtaining prior informed consent from the participants at the time of randomisation was impossible. 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 (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.

Table 5 Inclusion and exclusion criteria of the COMACARE trial (studies II-III)

Inclusion criteria	Exclusion criteria
Witnessed OHCA with VF or pulseless VT as initial rhythm	In-hospital cardiac arrest
ROSC 10-45 min	Initial rhythm PEA or asystole
Confirmed or suspected cardiac origin of the arrest	Cardiac arrest with confirmed or suspected non-cardiac etiology
Markedly impaired level of consciousness on arrival to ICU (GCS motor score < 5)	Probable withdrawal from active ICU care due to terminal illness or poor prognosis because of severely reduced functional status before cardiac arrest
Mechanical ventilation	Deferred consent impossible or unlikely (no known next of kin or relatives)
Deferred consent from next of kin possible or likely	Conscious patient or only mild impairment of consciousness on arrival to ICU (GCS motor score ≥ 5)
Active ICU care and TTM initiated	Confirmed or suspected acute or pre-existing intracranial pathology and/or increased ICP
	Age < 18 or > 80 years
	Pregnancy
	Severe oxygenation failure defined as PaO_2/FiO_2 < 100 mmHg upon ICU arrival and no improvement after optimization of mechanical ventilation
	Severe COPD

Abbreviations: OHCA, out-of-hospital cardiac arrest; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; ICP, intracranial pressure; ICU, intensive care unit; GCS, Glasgow Coma Scale; TTM, targeted temperature management; PaO_2, arterial oxygen tension; FiO_2, fraction of inspired oxygen; and COPD, chronic obstructive pulmonary disease.

Randomisation and blinding

All patients were randomised at the time of ICU arrival by a web-based randomisation system (Absolute Imaginary Software, Finland). A cryptographically strong random number generator with modulo bias eliminated was used to generate random numbers, and an unbiased Fisher-Yates (Durstenfeld) algorithm was used to shuffle the blocks. The randomisation was stratified based on 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, monitored vital parameters, the results of the ABG analyses, or daily obtained blood test results. However, as NIRS monitoring was not part of the routine post-resuscitation care at the study centres, the frontal rSO_2 results were not visible to the treating personnel. Moreover, the neurophysiologist analysing the EEG results and the neurologist evaluating the neurologic recovery of the participants were blinded to the study group allocations.

Interventions

The intervention targets are represented in Table 6. After ICU admission and randomisation, the ICU personnel was guided to target low-normal or high-normal $PaCO_2$, normal or moderately elevated PaO_2 and low-normal or high-normal MAP for 36 h from ICU admission or until the patient was extubated or ventilation was set to a spontaneous mode. The designated $PaCO_2$ level was targeted by adjusting the tidal volume and ventilation rate delivered by the ventilator. Normoxia or moderate hyperoxia were targeted by adjusting FiO_2 and PEEP levels on the ventilator.

Table 6 Intervention targets in the COMACARE trial (studies II-III)

Group	$PaCO_2$	PaO_2	MAP
1	4.5-4.7 kPa	10-15 kPa	65-75 mmHg
2	5.8-6.0 kPa	10-15 kPa	65-75 mmHg
3	4.5-4.7 kPa	20-25 kPa	65-75 mmHg
4	5.8-6.0 kPa	20-25 kPa	65-75 mmHg
5	4.5-4.7 kPa	10-15 kPa	80-100 mmHg
6	5.8-6.0 kPa	10-15 kPa	80-100 mmHg
7	4.5-4.7 kPa	20-25 kPa	80-100 mmHg
8	5.8-6.0 kPa	20-25 kPa	80-100 mmHg

Abbreviations: $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; and MAP, mean arterial pressure.

The ventilator adjustments were guided by ABG analyses performed at least every 3 hours. The results of the ABG analyses were corrected to each patient's actual temperature measured from inferior vena cava or the urinary bladder. End-tidal carbon dioxide ($EtCO_2$) monitoring was used as an additional guide in targeting the desired $PaCO_2$ level. In the normoxia group, peripheral oxygen saturation (SpO_2) was used as an additional guide, targeting an SpO_2 value of 95–98%. A volume-controlled or a pressure-controlled ventilation mode was used according to the treating clinician's preference.

The designated MAP level was targeted by using a continuous infusion of noradrenaline as needed. Hypovolemia was treated with fluid boluses according to the treating clinicians' preference. If low CO was confirmed or suspected, the use of an inotrope such as dobutamine or levosimendan was allowed. There were no pre-defined limits regarding the infusion rates of noradrenaline or inotropes. In order to meet the low-normal MAP target, the blood pressure was not lowered by any means other than sedation and/or pain medication. If MAP exceeded 140 mmHg or left ventricular systolic dysfunction was detected, the use of vasodilating agents to lower the blood pressure according to the treating clinicians' decision was allowed. All patients were treated with TTM at 33 °C or 36 °C according to the local ICU protocol and sedated as needed. Standard monitoring, care and investigations according to the local ICU protocol were used for all patients.

Except for moderate hyperoxia, all targeted $PaCO_2$, PaO_2, and MAP levels were within the recommendations of current guidelines [15,147]. Regarding $PaCO_2$, targeting such a narrow area on the lower or upper end of the normal range could increase the risk of intermittent hypocapnia or hypercapnia. However, with frequent ABG analyses taken at least every 3 hours and continuous $EtCO_2$ monitoring, the risk was not considered to be greater than in the patients receiving standard post-resuscitation care. Although the higher PaO_2 target was clearly outside the normal range, previous studies have not demonstrated harm from this level of hyperoxia, and there is some evidence suggesting that it could be beneficial instead [33,57]. Thus, both the researchers of the study and the ethical committee considered this intervention to be ethically justified. Regarding MAP, even a small deviation of blood pressure below the lower target of 65-75 mmHg would expose the patient to hypotension. However, with continuous direct arterial pressure monitoring and a dedicated nurse at the patients' side at all times, the risk was considered to be small and no different from patients treated with standard post-resuscitation care.

Outcomes

The primary outcome of the COMACARE trial was the NSE serum concentration at 48 h after CA. The main feasibility outcomes were the differences in $PaCO_2$, PaO_2 and MAP between the intervention groups. The pre-specified secondary outcomes were serum NSE concentrations at 24 h and 72 h after CA; serum S100B protein concentrations at 24 h, 48 h, and 72 h after CA; plasma cardiac troponin (TnT)

concentrations at 24 h, 48 h, and 72 h after CA; cerebral oxygenation (frontal rSO_2) measured by continuous NIRS monitoring during the first 48 h after admission to the ICU; results of continuous EEG monitoring for the first 48 h after admission to the ICU, interpreted by an experienced senior neurophysiologist blinded to the study group allocation; neurological outcome determined with the CPC scale at 6 months after CA (CPC 1–2 considered as good outcome and CPC 3-5 as poor outcome), determined by an experienced neurologist blinded to the 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 CA (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 oedema 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 details regarding the CA and resuscitation, were entered and saved in an electronic study database (Absolute Imaginary Software, Finland). SpO_2, heart rate, $EtCO_2$ and direct blood pressure measurements (systolic, diastolic and mean arterial pressures) via arterial cannula were done every 10 minutes and saved in a medically approved tablet computer (Arbor M1040, Taiwan; and S/5 collect software version 4.0, GE Healthcare, USA) connected to the patient monitor during the first 48 h after ICU admission. In case of technical difficulties, the values of these parameters were obtained later from the ICU software database (PICIS Clinical Solutions, USA). The ventilator settings were exported directly from the ventilators and saved in a USB drive after the intervention. In case this was not possible due to technical problems, the ventilator values were entered manually into the electronic database.

The blood samples for the ABG analyses were obtained via arterial cannula and analysed on-site as part of routine ICU care. The results of the ABG analyses, corrected to the patient's actual temperature, were entered manually into the electronic study database. The doses of sedative and vasoactive drug infusions were also entered manually into the database.

The blood samples for the analyses of NSE, S100B and TnT concentrations were obtained via arterial cannula upon ICU admission and 24 h, 48 h and 72 h after CA. In the Finnish centres, the samples were centrifuged (2000 G, 10 min) and frozen at –70 °C at the hospital laboratory, and the determination of NSE, S100B, and TnT was performed using a COBAS e601 line (Hitachi High Technology Co, Japan) with an electro chemiluminescent immunoassay kit (Roche Diagnostics GmbH, Germany) in January 2018. 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. Because haemolysis can alter the NSE results, all serum samples obtained in the Finnish centres were tested for haemolysis using the Roche haemolysis index. All samples with significant haemolysis ($n = 7$), defined as more than 500 mg of free Hb per litre, were excluded from the NSE analyses. In the samples taken at the Danish centre ($n = 26$), the NSE concentration was analysed immediately and haemolysis was not assessed.

Frontal rSO_2 was measured with continuous NIRS during the first 36-48 h of intensive care using a Covidien INVOS 5100C device (Covidien Company, USA). Two non-invasive skin sensors, one to each side, were attached to the patient's forehead by a study nurse according to the instructions of the manufacturer. Because NIRS monitoring was not part of routine care in the participating ICUs, the treating personnel were blinded from its results, and the rSO_2 measurements did not affect patient care. The rSO_2 values, approximately 10 measurements per minute from both sensors, were saved to a USB memory stick attached to the NIRS device.

Continuous four-channel EEG was recorded with a GE Carescape module (GE Healthcare, USA) connected to the patient monitor during the first 48 h of ICU care or until consciousness was regained. The EEG recordings were saved to the tablet computer using the S/5 collect software version 4.0 (GE Healthcare, USA). One senior neurophysiologist blinded to the study group allocations analysed all the EEG recordings after the patient recruitment was completed and categorised them into three groups according to the degree of abnormality (mild, moderate or severe, as proposed by Crepeau et al [148] at the beginning and at the end of the intervention. An experienced senior neurologist blinded to the study group allocations contacted all hospital survivors or their surrogates by telephone at six months after CA and determined their functional statuses using the CPC scale.

Statistical methods

Categorical data between the intervention groups were compared with a chi-square test for association. The normality of the continuous data was tested with a Kolmogorov-Smirnov test and the data with a normal distribution were compared with an independent-samples t-test and the data with a non-normal distribution were compared with a Mann–Whitney U test.

Regarding $PaCO_2$ and PaO_2, the intervention time was divided into 3 h periods starting at the time of ICU admission and the mean $PaCO_2$ and PaO_2 was calculated for each period for each patient. The median of these 3 h means was then compared between the low-normal and high-normal $PaCO_2$ groups and normoxia and moderate hyperoxia groups over time using a generalized mixed model with a compound-symmetry covariance matrix. Regarding MAP, the intervention time was divided into 1 h periods starting at the time of ICU admission and the median MAP was calculated for each period for each patient. These 1 h medians were then compared between the low-normal and high-normal MAP groups over time using a

generalized mixed model with a compound-symmetry covariance matrix.

The NSE serum concentrations at 48 h in the different intervention groups were compared using a Mann–Whitney U test. The NSE, S100B and TnT concentrations and frontal rSO_2 values over time were compared using a generalized mixed model with a compound-symmetry covariance matrix. The distributions of EEG abnormalities (mild, moderate, or severe), 30-day mortality and the six-month CPC results between the groups were compared with a Chi-square test for association.

The interaction effect of the $PaCO_2$, PaO_2 and MAP targets with the TTM, $PaCO_2$, PaO_2 and MAP targets on the NSE results at 48 h was analysed with univariate analysis of variance. The interaction effect of the $PaCO_2$, PaO_2 and MAP targets with the TTM, $PaCO_2$, PaO_2 and MAP targets on the CPC results at 6 months was analysed with a binary logistic regression model.

All statistical analyses were done with the SPSS Statistics version 24.0 (IBM Corporation, USA).

Neuroprotect trial

The Neuroprotect trial was a randomised clinical trial aiming to investigate whether an early goal-directed haemodynamic optimisation during the first 36 of post-resuscitation care would reduce HIE and improve outcomes when compared with standard care. A total of 112 OHCA patients in two hospitals in Belgium were randomly assigned to targeting either MAP 65 mmHg or MAP 85-100 mmHg during the first 36 h after ICU admission [146]. In the higher MAP group, there was an additional target of SvO_2 65-75%. All adult patients who were resuscitated from OHCA with a presumed cardiac cause and who remained unconscious (GCS < 8) at hospital admission were screened for eligibility. The exclusion criteria were suspected or confirmed intracranial bleeding or stroke, known limitations in therapy or a Do Not Resuscitate -order, known disease compromising 180 day survival, CPC 3-4 before CA, previous stroke or TIA, MRI incompatible cardiac or neurosurgical device, systolic blood pressure < 90 mmHg on norepinephrine > 1 µg/kg/min, open chest, extracorporeal membrane oxygenation (ECMO) initiated, or pregnancy. Written informed consent was obtained from a next of kin, or if unavailable, a procedure for inclusion in emergency situations was applied. A definitive post-hoc consent form was ultimately obtained from all patients who recovered sufficiently to make independent decisions. SvO_2 65-75% was targeted with optimising fluid status, maintaining the Hb level over 100 g/l, treating excessive bradycardia (HR < 40/min) and infusing dobutamine as necessary starting with 5 µg/kg/min. The designated MAP level was targeted with a continuous infusion of noradrenaline as needed. All patients were treated with standard post-CA care including intubation, mechanical ventilation, sedation, and TTM at 33 °C.

The primary outcome of the Neuroprotect trial was the extent of anoxic brain injury, measured with the percentage of ischaemic voxels with an apparent diffusion coefficient below 650.10^{-6} mm^2/s on diffusion weighted magnetic resonance

imaging (MRI) performed 4-6 days after CA. The secondary outcomes were favourable neurological outcome at ICU discharge and at 180 days defined as CPC 1-2, length of ICU stay, duration of mechanical ventilation, need for tracheostomy, NSE concentrations during days 1-5, creatinine concentrations and diuresis during days 1-5, 6 minute walking distance at hospital discharge, and all-cause mortality at 180 days.

Post hoc analyses

Association of cerebral oxygenation with NSE and neurological outcome

The first post hoc analysis (IV) investigated the association of frontal rSO_2 during the first 36 h of ICU care after OHCA with NSE concentrations at 24 h, 48 h, and 72 after CA; and the association of rSO_2 with dichotomised neurological outcome (CPC 1-2 considered as good outcome and CPC 3-5 as poor outcome) at six months. In addition, the association of NSE concentration with good and poor neurological outcome was assessed. The methods of the data collection for frontal rSO_2, NSE concentrations and neurological outcome have been described above. The median NSE concentrations at 48 h after CA between patients with good and poor neurological outcome at 6 months were compared using a Mann–Whitney U test. The median frontal rSO_2 during the first 36 h of intensive care was calculated for each patient and the association between median rSO_2 and NSE concentrations at 24, 48 and 72 h was assessed using a scatterplot and a Spearman's rank-order correlation. The 36-h median rSO_2 between patients with good and those with poor outcome were compared using a Mann–Whitney U test. The rSO_2 over time between patients with good and those with poor outcome was compared using a generalized mixed model with a compound symmetry covariance matrix. A binary logistic regression model was used to ascertain the effects of baseline factors and rSO_2 on the likelihood of good neurological outcome. The factors that were significantly associated with prognosis ($p < 0.05$) in univariate analysis were selected. These factors were age, bystander-initiated resuscitation, delay from collapse to ROSC, and Acute Physiology and Chronic Health Evaluation (APACHE) II score. In addition, the cohort was divided into tertiles according to the lowest 60-min median rSO_2 during the 36-h period, and the probability for a good outcome with 95% confidence interval was calculated for each tertile. The area under the receiver operating characteristic curve with 95% confidence interval was calculated for the lowest 60-min median rSO_2 to predict good outcome in each tertile.

Arterial pressure and myocardial damage in AMI patients

The second post hoc analysis (V) was a pooled analysis of two trials: the COMACARE trial and the Neuroprotect trial, a randomised clinical trial investigating the effect of

early goal-directed haemodynamic optimisation on brain injury in patients resuscitated after OHCA [146]. The aim was to investigate the possible association between MAP level and the extent of myocardial injury in a subgroup of patients with AMI and vasopressor dependent hypotension.

All COMACARE and Neuroprotect patients with AMI and vasopressor dependent hypotension were included in the pooled analysis. Because chest pain could not be assessed and practically all CA patients have some form of ECG abnormalities and elevated cardiac troponin levels, the universal criteria for AMI could not be used. Instead, AMI was defined as either ST-elevations in the ECG (STEMI) or as a non-STEMI with identification of a clear culprit lesion (a coronary lesion with at least 70% stenosis and the presence of characteristics of plaque disruption) in coronary angiography performed within 2 hours after hospital admission. The primary endpoint was myocardial infarct size assessed by the area under the 72-hour TnT curve. TnT was measured at hospital admission and at 24, 48 and 72 hours after CA in both trials. In the Neuroprotect trial, there was an additional troponin measurement at 5 hours. Additional TnT measurements were made during the first 72 h according to local protocol and orders by the treating clinician, and all these results were included in the final analyses. The determination of the TnT concentration was performed using a COBAS e601 line (Hitachi High Technology Co, Tokyo, Japan) with an electro chemiluminescent immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany).

The area under the 72-hour TnT curve was compared between both groups using a Van Elteren test that included the study (Neuroprotect/COMACARE) as a stratification factor. For missing TnT data of patients who died before 72 h, the missing value was replaced with the highest TnT in the corresponding treatment group. Missing data from patients surviving beyond 72 h were imputed by regression analysis on the logarithmically transformed TnT values. In cases where the TnT measurement was missing at the time of ICU admission, the value was imputed with the median value observed in the study at ICU admission. Longitudinal data (MAP, diastolic blood pressure, heart rate, dose norepinephrine and dobutamine) were analysed using a generalized estimating equation model for normally distributed data that included factors for time (included as a categorical variable), treatment, study and their interactions. The model included an exchangeable working correlation matrix to account for within-patient correlations. Differences in the profiles over time between the two treatment groups were assessed by the interaction. SPSS Statistics version 24.0 (IBM Corporation, USA), SAS version 9.4 (SAS Institute Inc, USA) and SAS/STAT version 14.2 (SAS Institute Inc, USA) were used for statistical analyses.

Results

The first patient of the COMACARE trial was randomised on 22 March 2016 and the recruitment was completed by 3 November 2017. The 6-month follow-up of the last patient was completed by 3 May 2018. The flowchart demonstrating patient enrolment and group allocation is presented in Figure 1. The baseline characteristics and resuscitation-associated factors were comparable between the groups (Table 7). Overall, 78 of 120 patients (65%) had good neurological outcome (CPC 1-2) at six months. Three patients had severe cerebral disability (CPC 3) and there were no patients in coma or vegetative state (CPC 4). At the end of the 6-month follow-up, 39 (33%) patients had died. In 34 of the dead patients (87%) the cause of death was HIE. All of the dead patients except one died before 30 days after CA.

Feasibility outcomes

A clear separation in $PaCO_2$, PaO_2 and MAP was observed between the groups during the intervention (Figures 2-4). Minute ventilation was higher in the low-normal $PaCO_2$ group than in the high-normal $PaCO_2$ group. The median (interquartile range [IQR]) expiratory tidal volume per body weight and the median (IQR) ventilation rate were 5.8 (5.2–6.8) ml/kg and 12 (12–14) min^{-1} vs. 5.4 (4.8–5.9) ml/kg and 11 (10–12) min^{-1}, respectively. The median (IQR) FiO_2 and PEEP levels were 35% (30–40%) and 7.2 (6.2–8.2) cmH_2O in the normoxia group and 50% (45–59%) and 8.2 (6.3–10.0) cmH_2O in the moderate hyperoxia group, respectively. The median (IQR) noradrenaline dose used was 0.05 (0.02–0.11) µg/kg/min in the low-normal MAP group and 0.13 (0.08–0.20) µg/kg/min in the high-normal MAP group.

Primary outcome

There were no significant differences in serum NSE concentrations at 48 h after CA between the intervention groups (Table 8). The median (IQR) serum NSE concentration at 48 h after CA was 18.8 (13.9–28.3) µg/l in the low-normal $PaCO_2$ group and 22.5 (14.2– 34.9) µg/l in the high-normal $PaCO_2$ group, $p = 0.400$; 22.3 (14.8–27.8) µg/l in the normoxia group and 20.6 (14.2–34.9) µg/l in the moderate hyperoxia group, $p = 0.594$; and 20.6 (15.2–34.9) µg/l in the low-normal MAP group and 22.0 (13.6– 30.9) µg/l in the high-normal MAP group, $p = 0.522$.

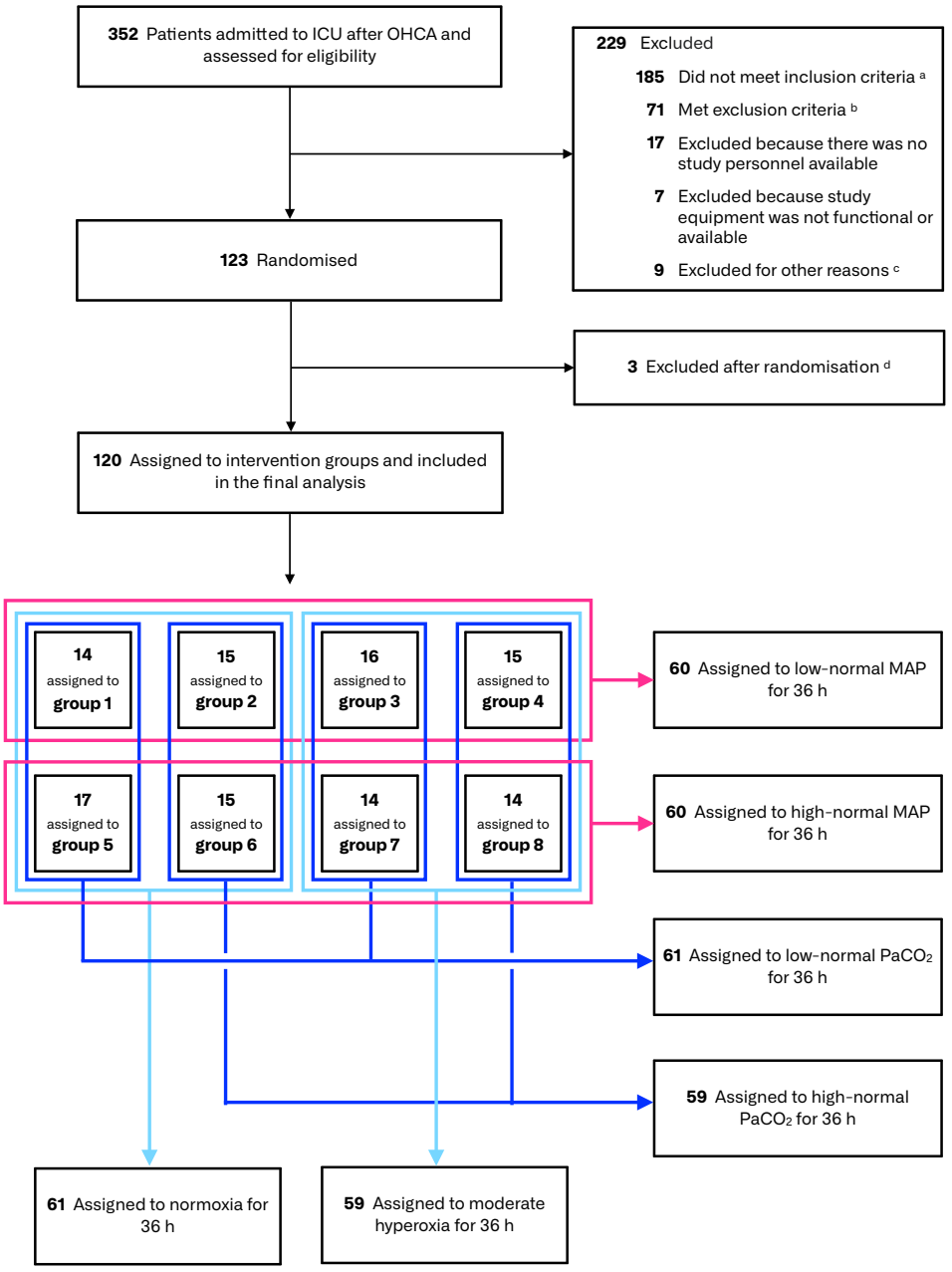

Figure 1 Screened, excluded and included patients in studies II-III and the allocations to different intervention groups

[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.

Secondary outcomes

No significant differences in the NSE, S100B or TnT concentrations over time were found between the low-normal and high-normal $PaCO_2$ groups, the normoxia and moderate hyperoxia groups or the low-normal and high-normal MAP groups (Figures 5-7). The frontal rSO_2 was significantly higher in the high-normal $PaCO_2$ and moderate hyperoxia groups than in the low-normal $PaCO_2$ and normoxia groups, respectively, $p < 0.001$ (Figures 8-9). In the low-normal and high-normal MAP groups the frontal rSO_2 values were comparable over time (Figure 10). The EEG grading at ICU admission and at the end of the intervention was comparable in all groups (Table 9). There were no significant differences between any of the groups regarding mortality at 30 days after CA, good neurological recovery (CPC 1–2) at 6 months after CA, the duration of intensive care or mechanical ventilation, or the frequency of the predefined SAEs (Table 8).

Association of cerebral oxygenation with NSE and neurological outcome

A total of 118 patients with continuous NIRS monitoring during the first 36 h of post-resuscitation intensive care were included in the analysis. Of these, 78 patients (66%) had CPC 1-2 and 40 patients (34%) CPC 3-5 at six months after CA (Figure 11). In univariate analysis, patient age, history of chronic heart failure, cardiac arrest location, bystander-initiated resuscitation, delay from collapse to ROSC, APACHE II score, and target temperature were significantly associated with the dichotomised neurological outcome at six months (Table 10). Median (IQR) serum NSE concentration at 48 h was 17.5 (13.4–25.0) µg/l in patients with good neurological outcome and 35.2 (22.6–95.8) µg/l in patients with poor neurological outcome, $p <$

Table 7 Baseline characteristics of the study population in the COMACARE trial

	Low-normal $PaCO_2$ group	High-normal $PaCO_2$ group
Number of patients	61	59
Demographic characteristics		
Age, mean ± SD, years	58 ± 11	61 ± 15
Male sex, n (%)	53 (87)	45 (76)
Weight, mean ± SD, kg	86 ± 17	83 ± 16
Neurologic function before cardiac arrest		
Normal, CPC score 1, n (%)	56 (92)	55 (93)
Some disability, CPC score 2, n (%)	5 (8)	4 (7)
Medical history		
Antihypertensive medication, n (%)	27 (44)	33 (56)
Chronic heart failure (NYHA class IV), n (%) [a]	2 (3)	0
Inhaled corticosteroids, n (%)	1 (2)	5 (8)
Inhaled bronchodilators, n (%)	2 (3)	6 (10)
Smoker, n (%) [b]	25 (41)	15 (25)
Cardiac arrest location		
Home, n (%)	34 (56)	26 (44)
Public place, n (%)	27 (44)	33 (56)
Resuscitation factors		
Bystander-initiated resuscitation, n (%)	50 (82)	48 (81)
Time to BLS, median (IQR), min	7 (5-9)	8 (6-10)
Time to ALS, median (IQR), min	9 (7-12)	10 (8-13)
Time to ROSC, median (IQR), min	20 (16-25)	21 (17-26)
Intubated during resuscitation, n (%)	30 (49)	27 (46)
Immediate interventional cardiology		
Pre-hospital thrombolysis, n (%)	2 (3)	2 (3)
Coronary angiography before ICU admission, n (%)	31 (51)	32 (54)
Clinical status on ICU admission		
GCS after ROSC, median (IQR) [c]	3 (3-3)	3 (3-3)
APACHE II score, median (IQR)	27 (24-30)	29 (25-33)
Pre-hospital cooling, n (%)	5 (8)	5 (8)
Dose of norepinephrine, mean ± SD, µg/kg/min	0.07 ± 0.1	0.07 ± 0.1
Time from ROSC to randomization, median (IQR), min	159 (130-204)	180 (143-216)
Targeted temperature management		
33 °C, n (%)	43 (70)	40 (68)
36 °C, n (%)	18 (30)	19 (32)

(studies II-III)

Normoxia group	Moderate hyperoxia group	Low-normal MAP group	High-normal MAP group
61	59	60	60
59 ± 13	60 ± 14	61 ± 11	58 ± 14
50 (82)	48 (81)	48 (80)	50 (83)
83 ± 15	86 ± 18	86 ± 19	83 ± 14
56 (92)	55 (93)	57 (95)	54 (90)
5 (8)	4 (7)	3 (5)	6 (10)
31 (51)	29 (49)	26 (43)	34 (57)
2 (3)	0 (0)	0	2 (3)
5 (8)	1 (2)	4 (7)	2 (3)
5 (8)	3 (5)	5 (8)	3 (5)
19 (31)	21 (36)	20 (33)	20 (33)
33 (54)	27 (46)	32 (53)	28 (47)
28 (46)	32 (54)	28 (47)	32 (53)
50 (82)	48 (81)	51 (85)	47 (78)
7 (6-10)	7 (6-9)	8 (6-10)	7 (5-9)
10 (8-12)	10 (7-12)	10 (7-12)	10 (7-12)
20 (16-25)	21 (16-27)	22 (16-27)	19 (15-25)
28 (46)	29 (49)	26 (43)	31 (52)
2 (3)	2 (3)	3 (5)	1 (2)
35 (57)	28 (47)	35 (58)	28 (47)
3 (3-3)	3 (3-3)	3 (3-3)	3 (3-3)
27 (24-31)	28 (25-31)	28 (24-32)	27 (24-31)
3 (5)	7 (12)	4 (7)	6 (10)
0.07 ± 0,1	0.07 ± 0,1	0.06 ± 0.08	0.08 ± 0.11
178 (139-216)	166 (135-192)	171 (148-214)	172 (128-204)
41 (67)	42 (71)	42 (70)	41 (68)
20 (33)	17 (29)	18 (30)	19 (32)

Table 7 Continued

Abbreviations: $PaCO_2$, arterial carbon dioxide tension; 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; BLS, basic life support; ALS, advanced life support; ROSC, return of spontaneous circulation; ICU, intensive care unit; GCS, Glasgow coma scale; and APACHE, acute physiology and chronic health evaluation.

[a] Data missing for 2 patients, [b] data missing for 13 patients, [c] data missing for 9 patients

0.001. Serum NSE concentration over time was significantly higher in patients with poor neurological outcome, $p < 0.001$ (Figure 12). No statistically significant association was observed between median frontal rSO_2 during the first 36 h in the ICU and serum NSE concentration at 48 h after CA, rs = – 0.08, $p = 0.392$ (Figure 13). Moreover, there was no association between median frontal rSO_2 during the first 36 h in the ICU and serum NSE concentrations at 24 h or 72 h after CA.

The median (IQR) frontal rSO_2 during the first 36 h of ICU care was 70.0% (63.5–77.0%) in patients with good neurological outcome and 71.8% (63.3–74.0%) in patients with poor neurological outcome, $p = 0.943$. There was no significant association between frontal rSO_2 over time and neurological outcome (Figure 14).

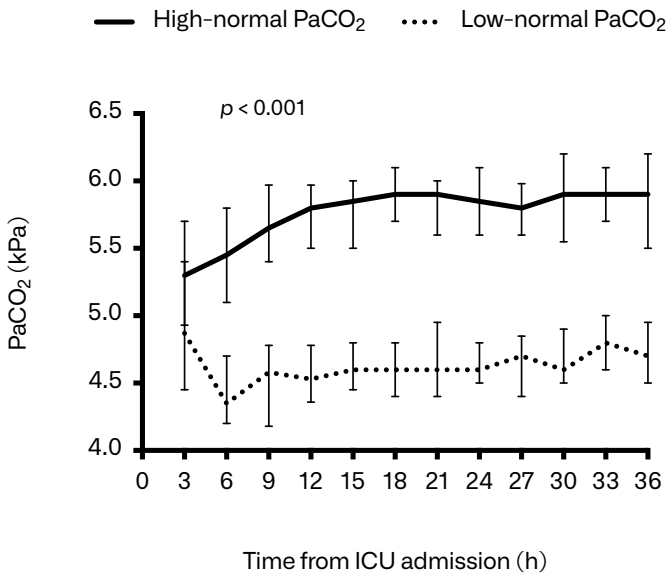

Figure 2 Median (inter-quartile range) arterial carbon dioxide tension ($PaCO_2$) during the intervention in patients assigned for targeting low-normal and high-normal $PaCO_2$ in study III

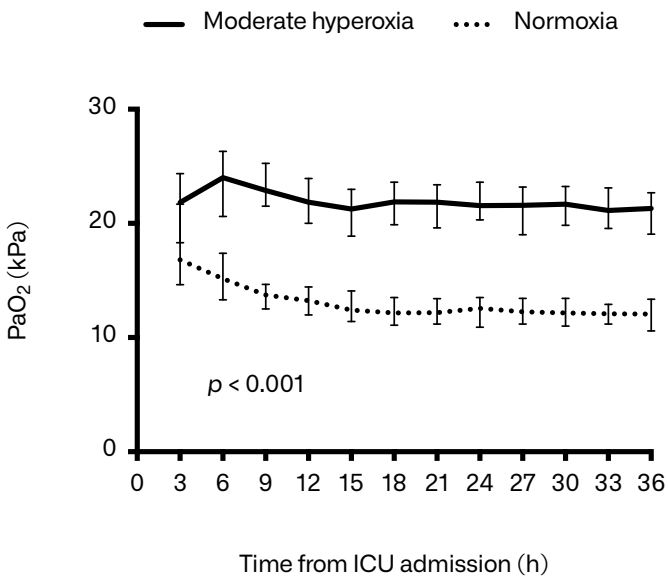

Figure 3 Median (inter-quartile range) arterial oxygen tension (PaO_2) during the intervention in patients assigned for targeting normoxia and moderate hyperoxia in study III

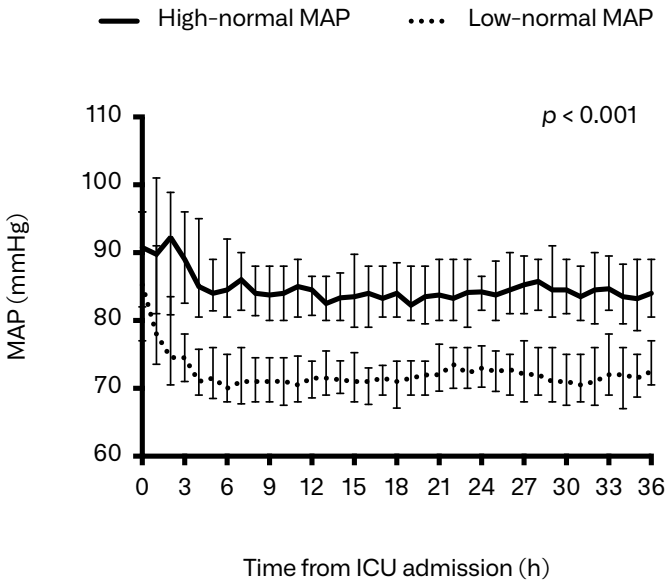

Figure 4 Median (inter-quartile range) mean arterial pressure (MAP) during the intervention in patients assigned for targeting low-normal and high-normal MAP in study II

Table 8 Primary and secondary outcomes after the interventions in the COMACARE trial (studies II-III)

	Low-normal $PaCO_2$ (n=61)	High-normal $PaCO_2$ (n=59)	*p*	Normoxia (n=61)	Moderate hyperoxia (n=59)	*p* value	Low-normal MAP (n=60)	High-normal MAP (n=60)	*p*
Primary outcome									
Median (IQR) NSE at 48 h after cardiac arrest, µg/l [a]	18.8 (13.9-28.3)	22.5 (14.2-34.9)	0.400	22.3 (14.8-27.8)	20.6 (14.2-34.9)	0.594	20.6 (15.2-34.9)	22.0 (13.6-30.9)	0.522
Secondary outcomes									
Good neurologic recovery (CPC 1-2) at 6 months after cardiac arrest, n (%)	43 (71)	35 (59)	0.200	42 (69)	36 (61)	0.368	37 (62)	41 (68)	0.444
Mortality 30 days after cardiac arrest, n (%)	15 (25)	23 (39)	0.090	18 (30)	20 (34)	0.605	20 (33)	18 (30)	0.695
Median (IQR) duration of intensive care, h [b]	92 (66-136)	104 (79-147)	0.120	97 (73-140)	100 (76-143)	0.810	107 (76-162)	94 (75-136)	0.283
Median (IQR) duration of mechanical ventilation, h [c]	63 (47-97)	75 (52-110)	0.589	61 (47-95)	74 (52-115)	0.211	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 (%)	0 (0)	1 (2)	0.307	1 (2)	0 (0)	0.323	1 (2)	0 (0)	0.315
Unexplained brain edema on CT scanning, n (%)	0 (0)	1 (2)	0.307	1 (2)	0 (0)	0.323	1 (2)	0 (0)	0.315
Severe ARDS (PaO_2/FiO_2 < 100 mmHg), n (%)	0 (0)	2 (3)	0.147	1 (2)	1 (2)	0.981	2 (3)	0 (0)	0.154

Abbreviations: $PaCO_2$, arterial carbon dioxide tension; 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; and FiO_2, fraction of inspired oxygen.

[a] Data missing for 1 patient, [b] data missing for 6 patients, [c] data missing for 3 patients

In the binary logistic regression model, the median frontal rSO_2 during the first 36 h in the ICU was not a statistically significant predictor of good outcome (adjusted odds ratio [OR] 0.99, 95% confidence interval 0.94–1.04, $p = 0.635$). In addition, the worst 60-min median frontal rSO_2 did not associate with good neurological outcome (Table 11).

Arterial pressure and myocardial damage in resuscitated patients with AMI

In total, 235 patients were randomised in the COMACARE (n = 123) and Neuroprotect (n = 112) trials. Of these, 93 patients did not have AMI and 17 patients did not undergo an immediate angiography, and they were excluded from the pooled analysis. In addition, the next of kin of four patients refused informed consent and there was one randomisation error. Thus, the pooled analysis consisted of 120 AMI patients of whom 58 were randomised to the MAP 80/85-100 mmHg group and 62 to the MAP 65 mmHg group (Figure 15). The pre-randomisation characteristics were comparable in both groups (Table 12). The majority of patients had ST segment elevation on the ECG upon hospital admission (79% in the higher MAP group vs. 85% in the lower MAP group, $p = 0.37$). All 120 patients underwent immediate angiography with an attempt for percutaneous intervention (PCI) of the culprit artery. The mean ± standard deviation (SD) time from ROSC to coronary angiography was comparable in both groups (73 ± 50 min in the higher MAP group vs. 66 ± 48 min in the lower MAP group, $p = 0.85$).

All 120 patients needed vasopressor support in order to achieve and maintain the designated MAP target. Patients assigned to the higher MAP group received significantly higher doses of norepinephrine as compared with the lower MAP group (median [IQR] 0.17 [0.08-0.30] µg/kg/min vs 0.08 [0.01-0.15] µg/kg/min, $p = 0.004$) and their MAP level was consistently higher during the intervention (Figure 16). The number of patients receiving dobutamine was comparable in both groups (14/58 (24%) vs 11/62 (18%), $p = 0.39$), but the mean ± SD dobutamine dose was significantly higher in patients assigned to the higher MAP group (4.5 ± 4.2 µg/kg/min vs. 3.7 ± 2.2 µg/kg/min, $p = 0.01$).

Myocardial damage, as quantified as the area under the 72-hour cardiac TnT curve, was greater in the lower MAP group than in the higher MAP group (median [IQR] 112 [44-340] µgh/l vs. 82 [25-166] µgh/l, $p = 0.04$, respectively) (Figure 17 and Table 13). The additional inotropic and vasopressor support in the higher MAP group did not increase the risk of a new onset CA (8/58 [14%] in the higher MAP group vs. 9/61 [15%] in the lower MAP group, OR 0.92 [95% CI 0.33-2.58], $p = 0.88$) or new onset atrial fibrillation (4/58 [7%] in the higher MAP group vs. 4/61 [7%] in the lower MAP group, OR 1.05 [95% CI 0.25-4.43], $p = 0.94$) (Table 13).

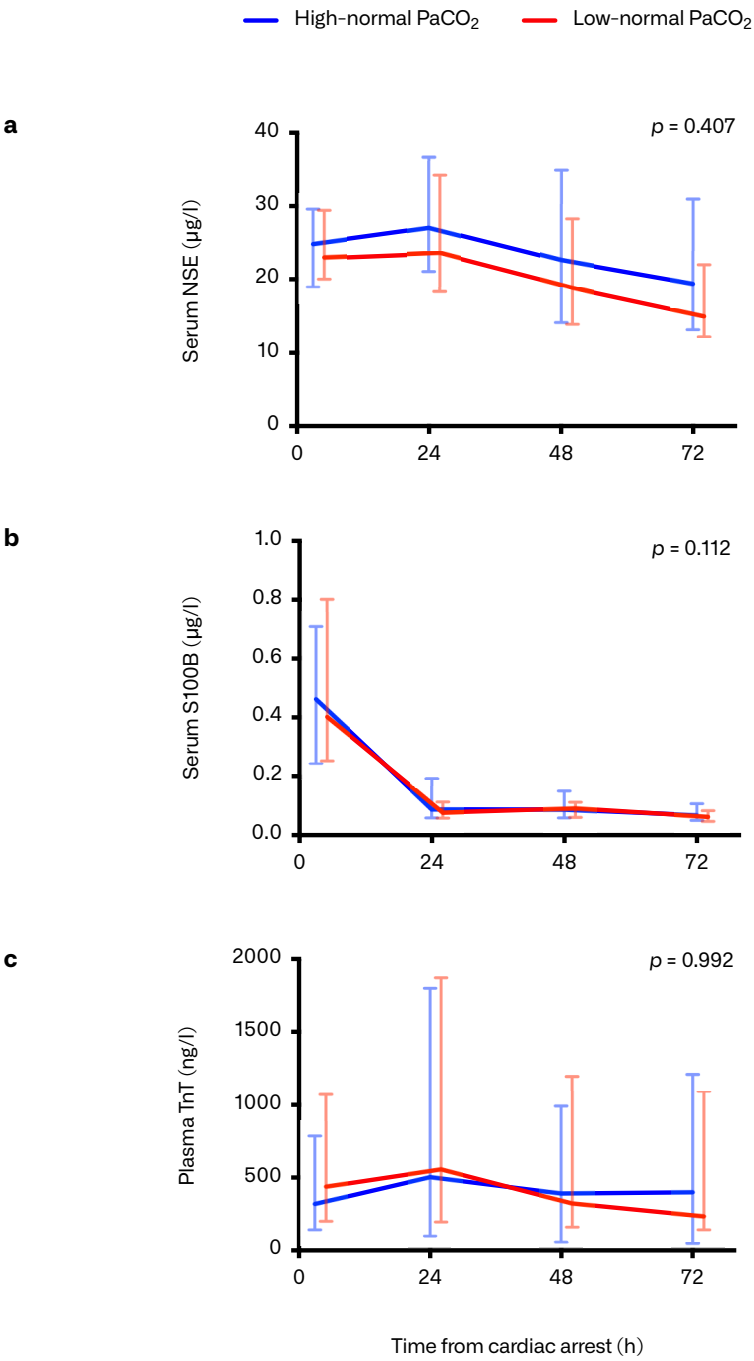

Figure 5 Baseline, 24 h, 48 h, and 72 h median (inter-quartile range) (**a**) serum neuron-specific enolase (NSE) concentrations, (**b**) serum S100B protein concentrations, and (**c**) plasma cardiac troponin (TnT) concentrations in patients assigned for targeting low-normal and high-normal arterial carbon dioxide tension ($PaCO_2$) in study III

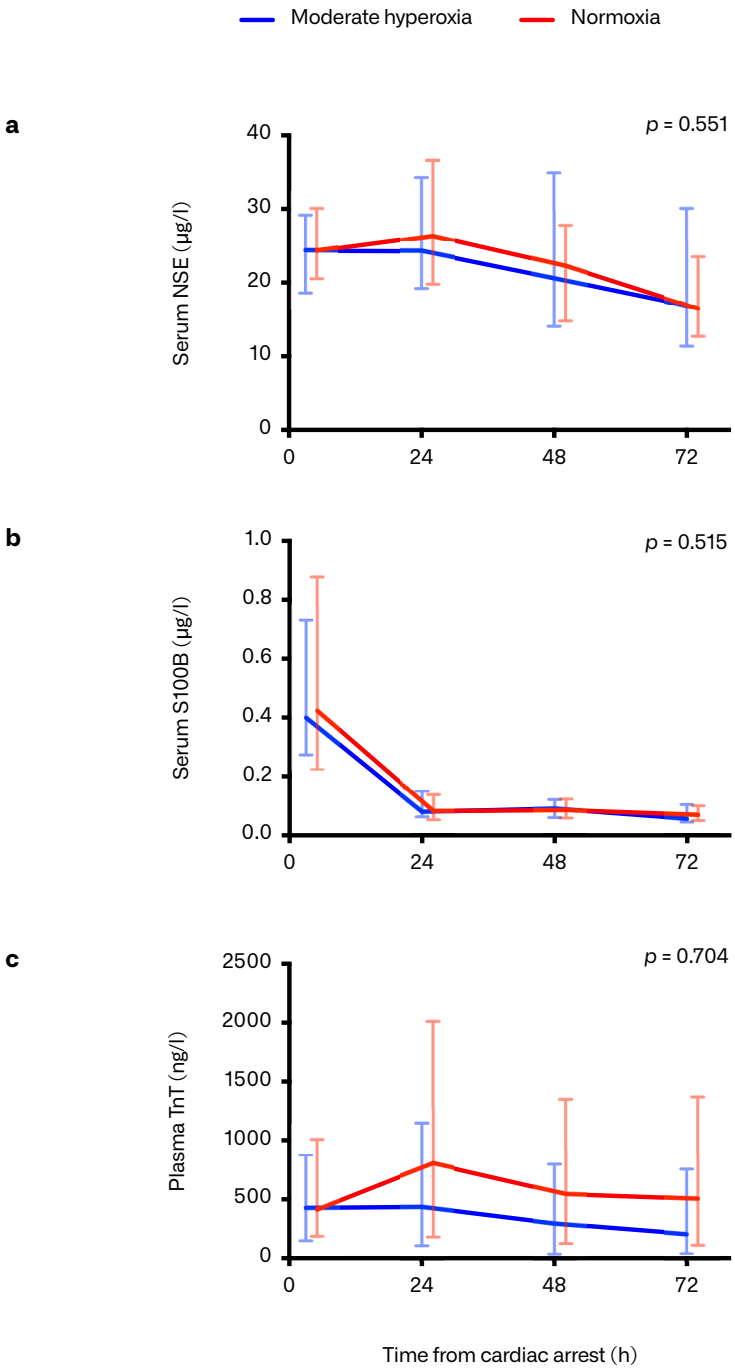

Figure 6 Baseline, 24 h, 48 h, and 72 h median (inter-quartile range) (**a**) serum neuron-specific enolase (NSE) concentrations, (**b**) serum S100B protein concentrations, and (**c**) plasma cardiac troponin (TnT) concentrations in patients assigned for targeting normoxia and moderate hyperoxia in study III

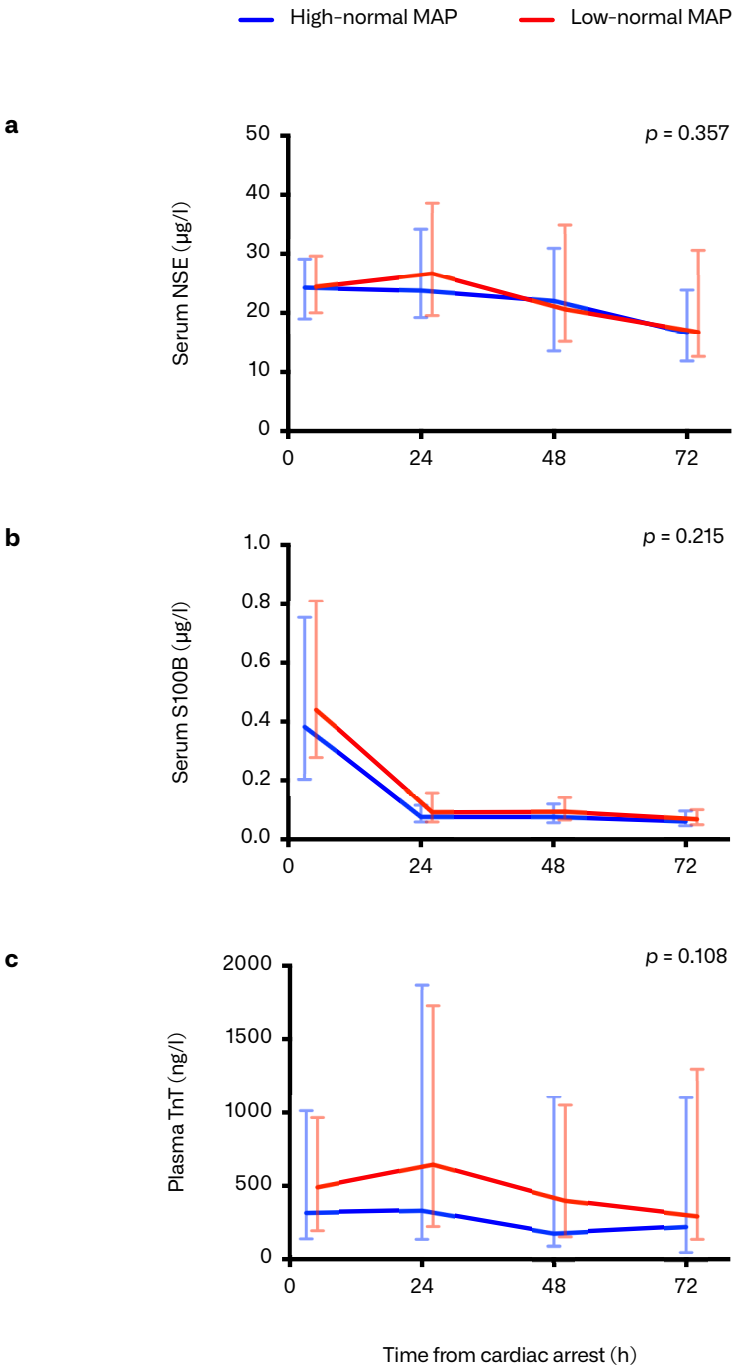

Figure 7 Baseline, 24 h, 48 h, and 72 h median (inter-quartile range) (**a**) serum neuron-specific enolase (NSE) concentrations, (**b**) serum S100B protein concentrations, and (**c**) plasma cardiac troponin (TnT) concentrations in patients assigned for targeting low-normal and high-normal mean arterial pressure (MAP) in study II

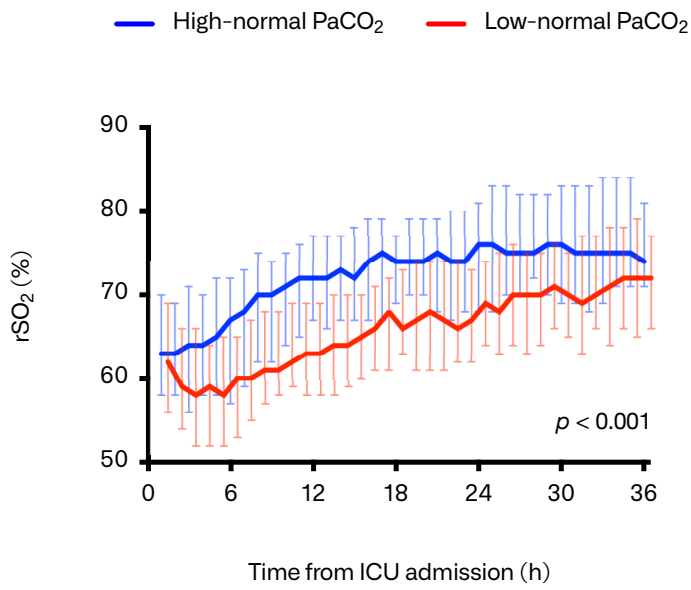

Figure 8 Median (inter-quartile range) frontal regional oxygen saturation (rSO_2) during the intervention in patients assigned for targeting low-normal and high-normal arterial carbon dioxide tension ($PaCO_2$) in study III

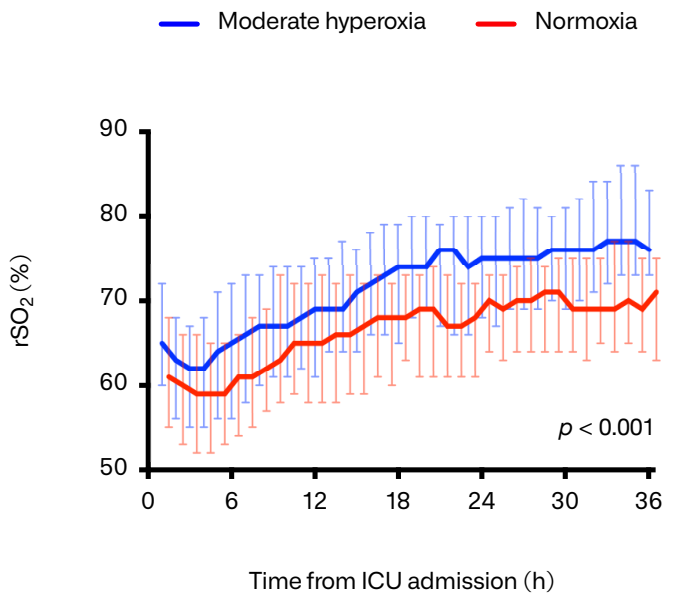

Figure 9 Median (inter-quartile range) frontal regional oxygen saturation (rSO_2) during the intervention in patients assigned for targeting normoxia and moderate hyperoxia in study III

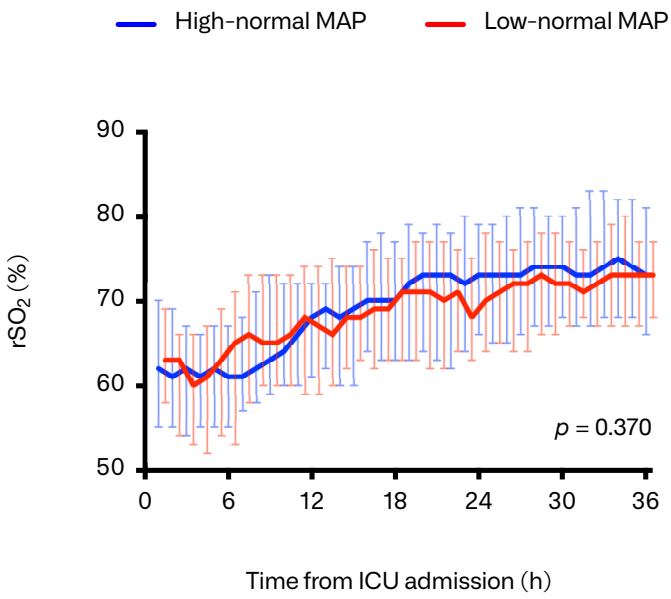

Figure 10 Median (inter-quartile range) frontal regional oxygen saturation (rSO_2) during the intervention in patients assigned for targeting low-normal and high-normal mean arterial pressure (MAP) in study II

Table 9 Number of patients (%) in each EEG grading category in the intervention groups at ICU admission and at the end of the intervention in the COMACARE trial (studies II-III)

	EEG-grade[1]	Low-normal $PaCO_2$	High-normal $PaCO_2$	Normoxia	Moderate hyperoxia	Low-normal MAP	High-normal MAP
ICU admission	1	17 (29)	14 (24)	19 (32)	12 (20)	12 (20)	19 (32)
	2	3 (5)	2 (3)	1 (2))	4 (7)	2 (3)	3 (5)
	3	39 (66)	43 (73)	39 (66)	43 (73)	45 (75)	37 (62)
		p = 0.710		p = 0.167		p = 0.278	
End of the intervention	1	43 (73)	35 (59)	43 (73)	35 (59)	39 (65)	39 (65)
	2	3 (5)	4 (7)	4 (7)	3 (5)	3 (5)	4 (7)
	3	13 (22)	20 (34)	12 (20)	21 (36)	17 (28)	16 (27)
		p = 0.294		p = 0.181		p = 0.917	

Abbreviations: EEG, electroencephalography; $PaCO_2$, arterial carbon dioxide tension and ICU, intensive care unit.

[1] 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).

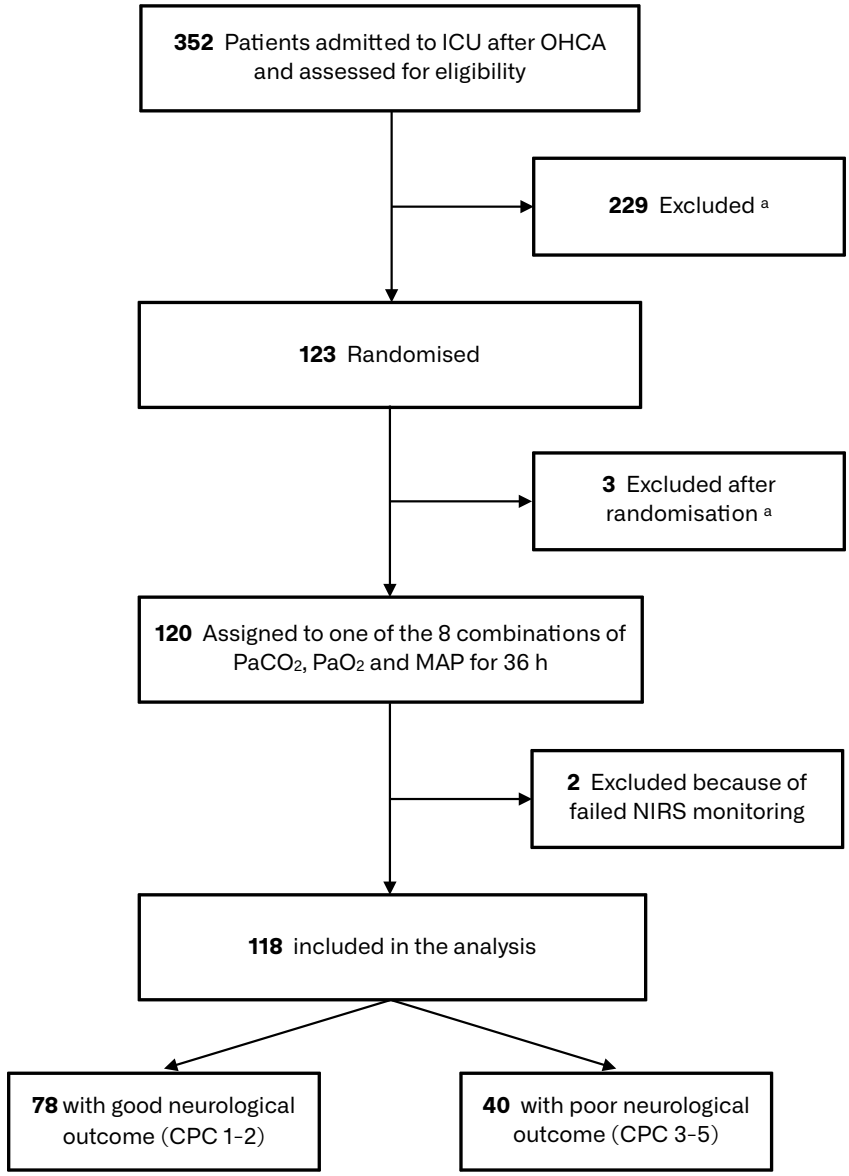

Figure 11 Screened, excluded and included patients in study IV and neurological outcome at six months after cardiac arrest

[a] Reasons for exclusion are represented in detail in Figure 1

Abbreviations: ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; $PaCO_2$, arterial carbon dioxide tension, PaO_2, arterial oxygen tension; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy and CPC, Cerebral Performance Category.

Table 10 Baseline characteristics of the study population in study IV according to good (CPC 1-2) or poor (CPC 3-5) neurological outcome at six months after cardiac arrest

	CPC 1-2	CPC 3-5	p value
Number of patients	78	40	
Demographic characteristics			
Age, mean ± SD, years	58 ± 13	63 ± 13	0.018
Male sex, n (%)	65 (83)	31 (78)	0.441
Weight, mean ± SD, kg	84 ± 16	86 ± 19	0.932
Neurologic function before cardiac arrest			0.582
Normal, CPC score 1, n (%)	72 (92)	38 (95)	
Some disability, CPC score 2, n (%)	6 (8)	2 (5)	
Medical history			
Antihypertensive medication, n (%)	36 (46)	23 (58)	0.243
Chronic heart failure (NYHA class IV), n (%) [a]	0 (0)	2 (5)	0.046
Inhaled corticosteroids, n (%)	1 (3)	5 (8)	0.360
Inhaled bronchodilators, n (%)	5 (6)	3 (8)	0.824
Smoker, n (%) [b]	25 (32)	15 (38)	0.161
Cardiac arrest location			0.038
Home, n (%)	33 (42)	25 (63)	
Public place, n (%)	45 (58)	15 (38)	
Resuscitation factors			
Bystander-initiated resuscitation, n (%)	68 (87)	29 (73)	0.048
Time to basic life support, median (IQR), min	7 (6-9)	8 (6-10)	0.672
Time to advanced life support, median (IQR), min	9 (7-11)	11 (7-13)	0.131
Time to ROSC, median (IQR), min	17 (14-22)	25 (21-31)	< 0.001
Intubated during resuscitation, n (%)	31 (40)	26 (65)	0.009
Immediate interventional cardiology			
Pre-hospital thrombolysis, n (%)	2 (3)	2 (5)	0.489
Coronary angiography before ICU admission, n (%)	37 (48)	24 (60)	0.196
Clinical status on ICU admission			
GCS after ROSC, mean ± SD, min [c]	4 ± 2	3 ± 0	< 0.001
APACHE II score, median (IQR)	27 (24-29)	30 (26-34)	0.014
Pre-hospital cooling, n (%)	9 (12)	1 (3)	0.095
Dose of norepinephrine, mean ± SD, µg/kg/min	0.07 ± 0.1	0.06 ± 0.1	0.712
Time from ROSC to randomisation, median (IQR), min	173 (134-216)	170 (141-202)	0.874
Targeted temperature management			0.004
33 °C, n (%)	61 (78)	21 (53)	
36 °C, n (%)	17 (22)	19 (48)	

Table 10 Continued

Abbreviations: 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]; SD, standard deviation; IQR, inter-quartile range; NYHA, New York Heart Association; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; GCS, Glasgow coma scale; ROSC, return of spontaneous circulation; and APACHE, acute physiology and chronic health evaluation.

[a] Data missing for 2 patients, [b] data missing for 13 patients, [c] data missing for 9 patients

Table 11 The probability for a good outcome (CPC 1-2) and the area under the receiver operating characteristics curve for the lowest 60-minute median rSO_2 to predict good outcome overall and in tertiles based on the lowest 60-minute median rSO_2 during the first 36 h in ICU in study IV

		CPC 1-2, % (95% CI)	AUC (95% CI)
All patients		66.1 (57.3-74.2)	0.524 (0.416-0.631)
Tertile group according to the lowest 60 min median rSO_2	1	68.3 (53.2-80.9)	0.544 (0.353-0.735)
	2	60.0 (44.6-74.1)	0.520 (0.337-0.702)
	3	70.3 (54.4-83.1)	0.594 (0.389-0.800)

Abbreviations: CPC, Cerebral Performance Category; rSO_2, regional cerebral oxygen saturation; ICU, intensive care unit; CI, confidence interval; AUC, area under the curve.

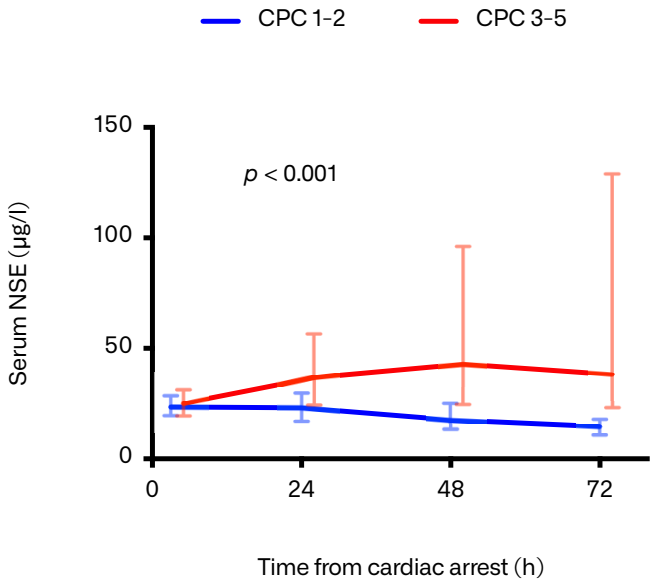

Figure 12 Baseline, 24 h, 48 h, and 72 h median (inter-quartile range) serum neuron-specific enolase (NSE) concentrations in patients with good (Cerebral Performance Category [CPC] 1-2) and poor (CPC 3-5) neurological outcome in study IV

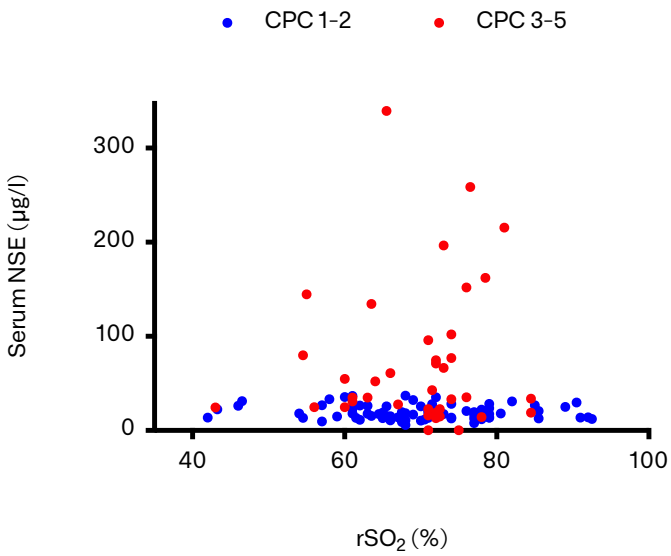

Figure 13 Scatter plots of serum neuron-specific enolase (NSE) concentration at 48 h after cardiac arrest vs. median regional cerebral oxygen saturation (rSO_2) during the first 36 h in intensive care unit in patients with good (Cerebral Performance Category [CPC] 1-2) and poor (CPC 3-5) neurological outcome in study IV

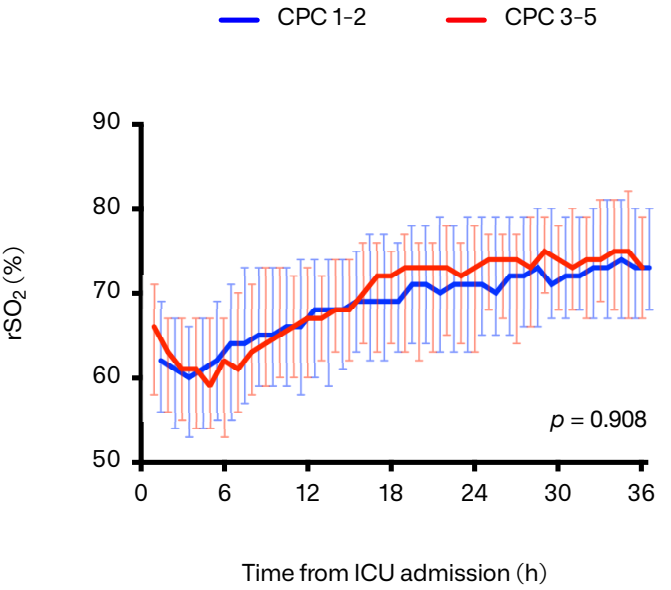

Figure 14 Median (inter-quartile range) regional cerebral oxygen saturation (rSO_2) during the first 36 h of intensive care in patients with good (Cerebral Performance Category [CPC] 1-2) and poor (CPC 3-5) neurological outcome in study IV

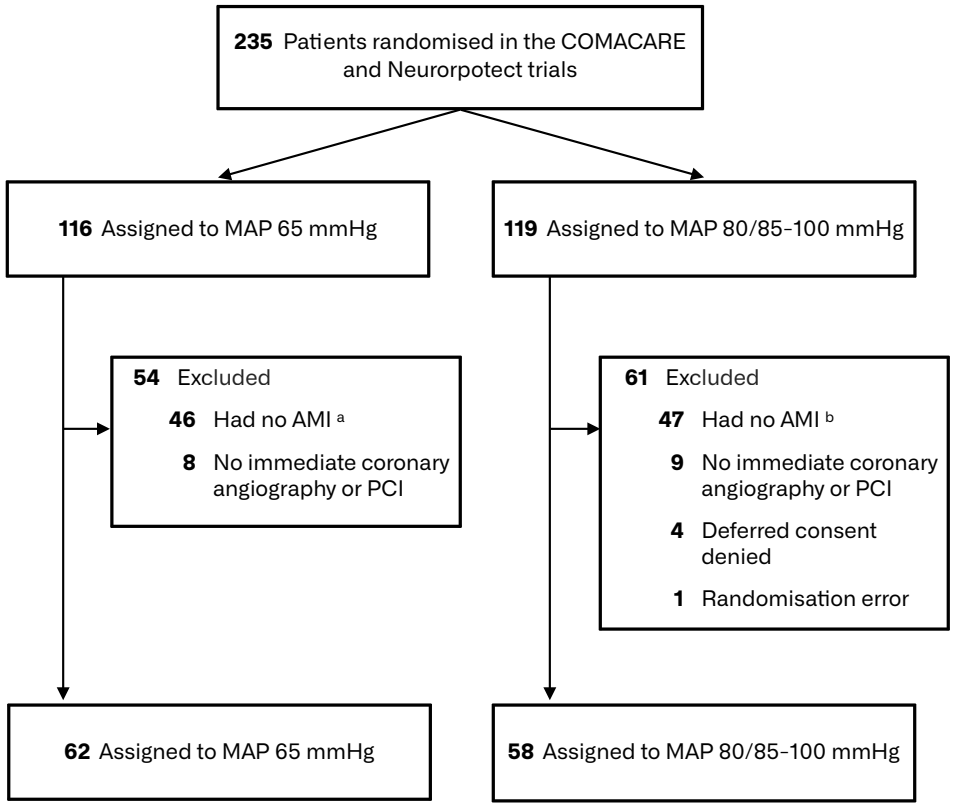

Figure 15 Screened, excluded and included patients in study V and allocation to different MAP arms

[a] Reasons for cardiac arrest in patients not meeting AMI criteria were as follows: arrhyhtmia (n=37), hypoxia (n=3), intracranial hemorrhage (n=1), pulmonary embolism (n=1), cause unclear (n=4).

[b] Reasons for cardiac arrest in patients not meeting AMI criteria were as follows: arrhyhtmia (n=36), hypoxia (n=8), stroke (n=1), aortic dissection (n=1), cause unclear (n=1).

Abbreviations: MAP, mean arterial pressure; AMI, acute myocardial infarction; and PCI, percutaneous coronary intervention.

Table 12 Baseline characteristics of the study population in study V

	COMA CARE	Neuroprotect	*p*	MAP 80/85-100 mmHg	MAP 65 mmHg	*p*
Number of patients	61	59		58	62	
Demographic characteristics						
Age, mean ± SD, years	60 ± 10	65 ± 11	0.31	62 ± 10	63 ± 11	0.48
Male sex, n (%)	54 (88)	50 (85)	0.69	51 (88)	53 (85)	0.69
Medical history						
Previous AMI, n (%)	8 (13)	9 (16)	0.68	5 (9)	12 (20)	0.11
Previous arrhytmia, n (%)	6 (10)	5 (9)	0.82	3 (5)	8 (13)	0.15
Arterial hypertension, n (%)	32 (47)	25 (46)	0.89	27 (50)	27 (44)	0.54
Betablocker, n (%)	11 (18)	11 (21)	0.75	10 (19)	12 (20)	0.81
Calcium channel blocker, n (%)	7 (12)	6 (11)	0.95	5 (9)	8 (13)	0.47
ACE-inhibitor / Angiotensin receptor blocker, n (%)	17 (28)	11 (21)	0.35	12 (22)	16 (27)	0.54
Diabetes mellitus, n (%)	9 (15)	4 (7)	0.19	8 (14)	5 (8)	0.33
COPD, n (%)	5 (8)	4 (7)	0.79	4 (7)	5 (8)	0.83
Stroke, n (%)	4 (7)	4 (7)	0.94	5 (9)	3 (5)	0.39
Cardiac arrest characteristics						
Public place, n (%)	34 (56)	33 (56)	0.98	32 (55)	35 (56)	0.89
Bystander-initiated resuscitation, n (%)	50 (82)	40 (69)	0.10	45 (79)	45 (73)	0.42
Initial rhythm			<0.01			0.87
Shockable (VF or pulseless VT), n (%)	61 (100)	46 (78)		52 (90)	55 (89)	
Non-shockable (PEA or asystole), n (%)	0 (0)	13 (22)		6 (10)	7 (11)	
Time to ROSC, min ± SD	21 ± 8	21 ± 12	0.86	21 ± 10	21 ± 10	0.70
Admission characteristics						
Pupillary reflexes present, n (%)	30 (59)	27 (55)	0.70	23 (52)	34 (61)	0.40
First lactate in ICU, median (IQR), mmol/l	1.9 (1.3-3.4)	2.9 (1.8-4.3)	0.03	2.35 (1.35-3.9)	2.25 (1.4-3.7)	0.70
SOFA score	8.43 ± 2.28	9.72 ± 2.86	0.19	9.09 ± 2.37	8.98 ± 2.86	0.13
TTM target			<0.01			0.89
33 °C, n (%)	45 (74)	59 (100)		50 (86)	54 (87)	
36 °C, n (%)	16 (26)	0 (0)		8 (14)	8 (13)	

Abbreviations: MAP, mean arterial pressure; SD, standard deviation; AMI, acute myocardial infarction; ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; ICU, intensive care unit; SOFA, sequential organ failure assessment; and TTM, targeted temperature management.

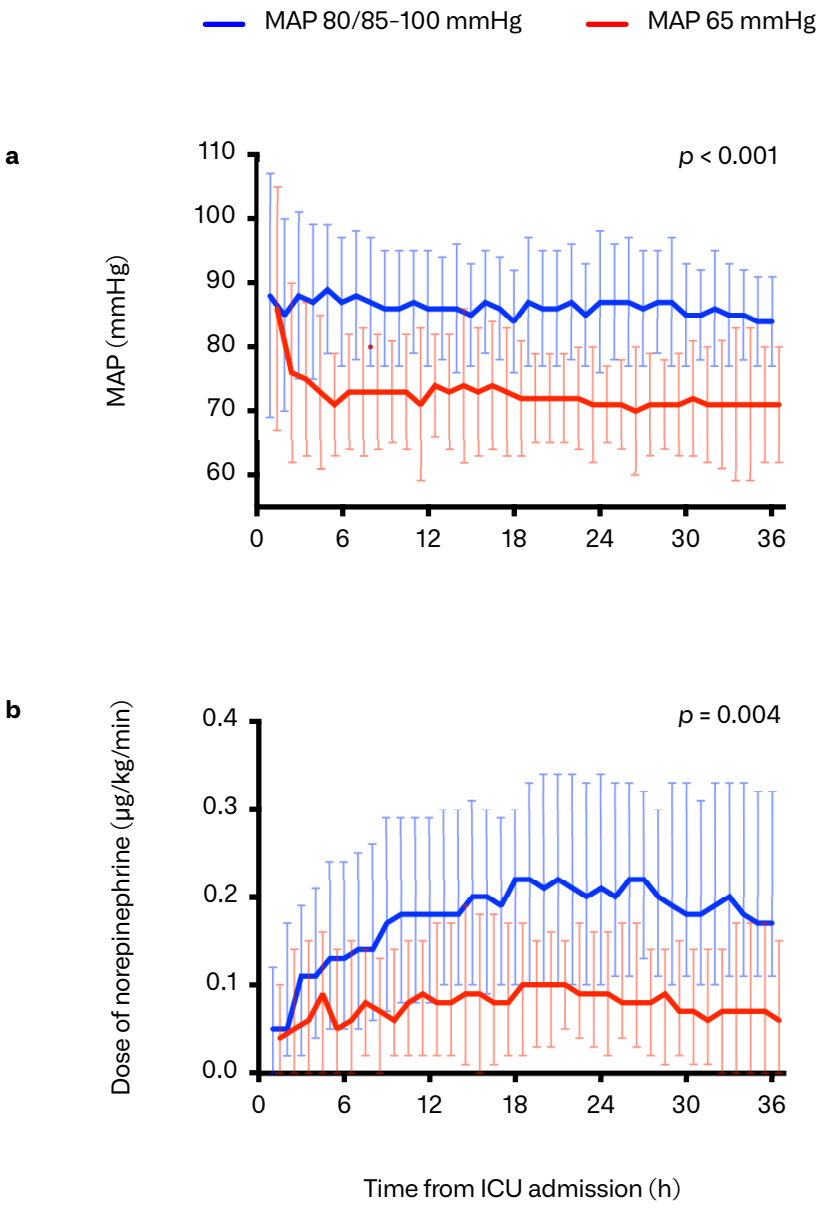

Figure 16 (**a**) Median (inter-quartile range [IQR]) mean arterial pressure (MAP) and (**b**) median (IQR) dose of nordadrenalin in the groups targeting MAP 65 mmHg and MAP 80/85-100 mmHg in study V

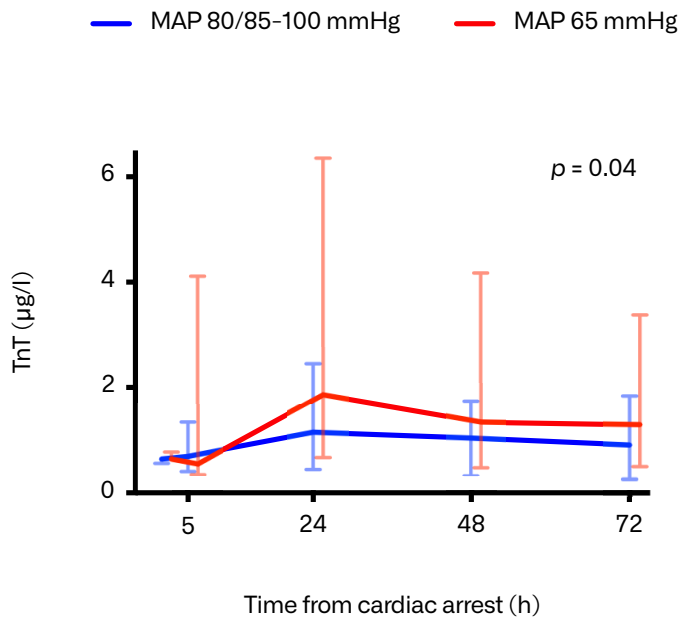

Figure 17 Median (inter-quartile range) cardiac troponin T (TnT) concentration during the first 72 h of intensive care in patients targeting mean arterial pressure (MAP) 65 mmHg and MAP 80/85-100 mmHg in study V

Table 13 Outcome measures in study V

	MAP 85/80-100 mmHg	MAP 65 mmHg	*p*
Median (IQR) area under the 72h TnT curve, µgh/l	82 (25-166)	112 (44-340)	0.04
New onset atrial fibrillation, n (%)	4 (7)	4 (7)	0.94
Recurrent cardiac arrest, n (%)	8 (14)	9 (15)	0.88
CPC 1-2 at 6 months after cardiac arrest, n (%)	37 (64)	33 (53)	0.24
All-cause mortality at 6 months after cardiac arrest, n (%)	21 (36)	25 (40)	0.63
Median (IQR) lenght of ICU stay (survivors), days	4.91 (3.70-7.00)	6.12 (4.98-10.0)	0.07
Median (IQR) duration of mechanical ventilation (survivors), days	2.47 (1.96-4.00)	3.62 (2.83-6.00)	0.07

Abbreviations: MAP, mean arterial pressure; IQR, inter-quartile range; TnT, cardiac troponin T; CPC, Cerebral Performance Category; and ICU, intensive care unit.

Discussion

Main results

The current study was a randomised pilot trial assessing the feasibility of targeting two different levels of $PaCO_2$, PaO_2, and MAP after OHCA, and comparing the effects of these interventions 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 $PaCO_2$, PaO_2 and MAP was feasible in comatose, mechanically ventilated patients, but it did not change the concentration of NSE at 48 h after CA or at any other studied time points. Concentrations of S100B protein and cardiac TnT and the EEG findings were also comparable between the intervention groups. Targeting high-normal $PaCO_2$ or moderate hyperoxia both increased cerebral oxygenation measured by NIRS but the clinical implications of this are unclear. In contrast, MAP level did not affect cerebral oxygenation. No significant association between cerebral oxygenation measured by NIRS and NSE concentrations at 48 h after CA was found, nor between cerebral oxygenation and neurological outcome at 6 months. In a subgroup of OHCA patients with AMI and vasopressor dependent hypotension, targeting a higher MAP of 80/85-100 mmHg was associated with smaller myocardial damage when compared with a MAP target of 65 mmHg.

Feasibility of targeting different $PaCO_2$, PaO_2, and MAP levels

One of the main purposes of this pilot study was to evaluate the feasibility of targeting two different levels of $PaCO_2$, PaO_2, and MAP in OHCA patients before a possible full-scale trial in the future. Although the relationship between MV and $PaCO_2$, FiO_2 and PaO_2, and noradrenaline dose and MAP may seem trivial, very little data on the tight control of these parameters in resuscitated patients exist. Before a larger randomised trial can be conceived, it is crucial to know whether the planned intervention is feasible with real patients in the established clinical setting.

In previous studies, only a weak correlation between prescribed MV and measured $PaCO_2$ has been found in CA patients soon after ROSC [37]. Moreover, inadvertent $PaCO_2$ derangements are common during post-resuscitation care despite the aim for normoventilation [98,32,33]. However, in a randomised controlled trial comparing mild hypercapnia with normocapnia, the investigators found that raising $PaCO_2$ over the

normal range by adjusting RR and TV was feasible [34]. In accordance with the results of this trial that was published during the patient recruitment of the current study, we found that targeting a very narrow range of $PaCO_2$ near the lower or upper limit of the normal range by adjusting RR and TV was possible and the separation between the low-normal and high-normal $PaCO_2$ groups was even better than expected. The use of continuous $EtCO_2$ monitoring and calculating the gap between $EtCO_2$ and $PaCO_2$ each time an ABG analysis was obtained was probably crucial in succeeding in such a tight $PaCO_2$ control. In the beginning of the intervention $PaCO_2$ was changing substantially in most patients even when MV was kept constant, and frequent ABG samples were needed to keep the $PaCO_2$ in the target range. This can be explained by the gradual opening of the atelectasis possibly formed during CPR, and the following changes in dead space ventilation and ventilation-perfusion mismatch. In addition, the haemodynamic instability seen in many patients during the early phase after ROSC might have contributed to the changing $PaCO_2$. After a few hours the $PaCO_2$ level stabilised in most patients, and only minimal changes in MV were needed to maintain it within the designated target.

Regarding oxygen, we found that maintaining PaO_2 within the target range by adjusting FiO_2 and PEEP was feasible, and the separation between the groups was clear. This was not surprising as the target ranges for normoxia and moderate hyperoxia were substantially wider when compared with those of low-normal and high-normal $PaCO_2$. Our results are in line with previous before-an-after studies comparing conservative versus conventional oxygen therapy in mechanically ventilated patients [100,101]. Importantly, in the current study, hypoxia (mean PaO_2 < 8 kPa during any 3-hour period) occurred in 11 (9%) patients, and only one of these patients had two 3-hour periods of hypoxia during the 36-hour intervention. There were no patients with severe hyperoxia (mean 3-hour PaO_2 > 40 kPa) at any time during the intervention.

In the current study, targeting a MAP level 65-75 mmHg or 80-100 mmHg was also feasible and a clear separation between the different blood pressure groups was achieved. This was somewhat expected, as goal-directed therapy aiming for a specific MAP level with fluids and vasoactive infusions has become routine in circulatory shock patients in intensive care. Noradrenaline was the vasopressor used in all patients, and inotropes were needed in a much lesser extent. While the effects of noradrenaline are mainly caused by its α_1-stimulating activity, it also affects CO in two different mechanisms: the increased vasoconstriction increases preload and thus cardiac index, and the $ß_1$-activity slightly increases cardiac contractility [149]. The result is a prompt raise in MAP and a moderate increase in CO without a significant raise in heart rate. In addition, noradrenaline decreases the need for volume replacement, helping to avoid excessive fluid administration with all its adverse effects. In accordance with a previous analysis of Finnish OHCA patients [87], the significantly higher dose of noradrenaline in the high-normal MAP group in the current study was not associated with increased risk for new-onset CA or severe arrhythmias. This finding was further supported by the results of the Neuroprotect trial [146]. Altogether, these results suggest that hypotension can be corrected, and MAP level

safely adjusted with a continuous infusion of noradrenaline during post-resuscitation intensive care.

Overall outcome

Overall, 68% of the patients randomised in studies II-III were alive at 30 days after CA, and 65% had good neurological outcome (CPC 1-2) at six months. This is a markedly good result when compared with previous reports regarding OHCA patients both internationally and in Finland. In a systematic review and meta-analysis of 79 studies reporting the outcomes of over 142 000 OHCA patients all over the world, the pooled survival rate to hospital discharge was 7.6% [150]. In the FINNRESUSCI study, the data of all OHCA patients in southern, central and eastern Finland were collected over 6 months, and the overall survival to hospital discharge was 19.9% [2].

Several reasons can explain the exceptionally good recovery rate in the current study. First, our study population was relatively selected as only patients with witnessed arrest, shockable initial rhythm and presumed cardiac origin were included. In addition, patients with ROSC over 45 min or age older than 80 years were excluded. To compare, in the FINNRESUSCI study, 45% of patients with bystander-witnessed arrest with shockable initial rhythm and presumed cardiac origin survived to hospital discharge [2]. Second, despite the multicentre design of the trial, 83 0f 120 patients (69%) included were admitted to Helsinki University Hospital, meaning that the CA probably occurred in the Helsinki metropolitan area where most patients are reached with short delays and there is an emergency medicine physician available already in the field. In rural areas the time for emergency medicine personnel to reach the patient is usually substantially longer, which inevitably affects the survival rate after OHCA. Third, the good quality of post-resuscitation intensive care in all centres taking part in the study may have affected the results. This means that the patients were admitted directly to ICU without delays in the emergency room, coronary angiography and interventions were immediately available and TTM was promptly initiated and the delay to target temperature was kept as short as possible. In addition, under normal circumstances, there was a highly trained ICU nurse by the bedside of each patient at all times. Finally, it is likely that several other factors related to the patient background, resuscitation process and post-resuscitation care exist but remain unknown so far.

Arterial carbon dioxide tension and HIE

Carbon dioxide increases cerebral perfusion and in previous experimental studies with animals, it has seemed to have antioxidant and anti-inflammatory properties after cerebral ischaemia [151]. In addition, CO_2 has been shown to act as a potent anticonvulsive agent both in animal and human experiments [27]. Based on these findings, it has been thought that hypercapnia might provide neuroprotection after CA by

helping to maintain adequate CBF, attenuating the inflammatory response caused by the systemic ischaemia-reperfusion injury, and decreasing the incidence of seizures. This hypothesis was supported by a randomised clinical trial where mild hypercapnia after CA and resuscitation reduced NSE concentrations and showed no evidence of harm when compared to normocapnia [34].

In the current study, we compared the effect of low-normal and high-normal $PaCO_2$ on biomarkers of cerebral and myocardial injury, cerebral oxygenation, epileptic activity, and neurological outcome. We found that targeting a very narrow range of $PaCO_2$ in mechanically ventilated patients was feasible, but it did not affect the severity of the developing HIE, as assessed by NSE concentrations during 24-72 h after CA or neurological recovery at 6 months. The EEG findings were also comparable with both investigated $PaCO_2$ levels. This was in contrast with some of the previous studies and also with our own hypothesis, but in line with a recent systematic review and meta-analysis of nine observational studies concluding that $PaCO_2$ has a U-shape association with survival and that both hypocapnia and hypercapnia can be detrimental during post-resuscitation care [40].

There are several reasons that can explain the neutral results of the current study regarding $PaCO_2$ and the extent of neurological damage. First, we compared $PaCO_2$ levels on both ends of the normal range, and it is possible that the absolute difference in $PaCO_2$ between the groups was not wide enough to demonstrate the possible impacts of higher CO_2 level in our patients. Second, hypercapnia has several adverse effects including increased ICP [22] and deepening acidosis [30], which are both major concerns in CA patients. The potential beneficial effects of high-normal $PaCO_2$ may have been counterbalanced with the adverse effects, and thus no difference in the outcome measures of the current study was seen. Third, the current study was not powered for mortality or neurological outcome, and it is possible that the sample size was too small to detect differences in the surrogate markers of cerebral injury as well. Finally, it may be that the beneficial effects of CO_2 seen in experimental models are not reproducible in the clinical setting with real CA patients, and that the level of CO_2 does not affect the development of the brain damage after all.

Arterial oxygen tension and HIE

Previous experimental studies have demonstrated that exposure to very high levels of oxygen after CA may increase ROS production and exacerbate the developing brain injury [51]. In several observational human studies, severe hyperoxia (PaO_2 > 40 kPa) has indeed been associated with poor outcome in resuscitated patients [53-56,58]. In contrast, moderate hyperoxia has been associated with better long-term neurological recovery and improved organ function [33,57]. The only randomised trial performed on the use of oxygen in OHCA patients before the current study compared FiO_2 30% vs. 100% immediately after ROSC. Although there was no statistically significant difference in NSE between the groups overall, the investigators saw an increase in NSE within a subgroup of patients exposed to 100% oxygen and not treated with TTM at

33 °C, suggesting a protective effect of hypothermia against the detrimental effects of hyperoxia exposure [52].

In the current study, we investigated the effect of normoxia vs. moderate hyperoxia on biomarkers of cerebral injury and several other outcomes after CA. This was the first randomised clinical trial comparing two different levels of PaO_2 during post-CA intensive care. We found that targeting a specific level of PaO_2 was feasible, but it did not affect NSE, S100B, or TnT concentrations, epileptic activity, or neurological outcome at 6 months. These findings suggest that moderate hyperoxia does not markedly affect the development of HIE as compared with normoxia. Importantly, we did not observe any signs of harm associated with moderate hyperoxia in OHCA patients.

Previous studies have observed a decrease in CBF and an increase in oxygen extraction soon after ROSC [152,153]. Based on these findings, it would be reasonable to think that increasing the oxygen content of the blood in CA patients could help to maintain adequate oxygen delivery to the injured brain and thus to avoid cerebral hypoxia during the phase of hypoperfusion. Indeed, a prospective observational study of Finnish OHCA patients suggested that the PaO_2 associated with the lowest mortality was around 20 kPa [33].

In the current study we found that cerebral oxygenation, as assessed with frontal rSO_2, was increased in the group targeting moderate hyperoxia, indicating that the oxygen delivery to the brain was increased with higher PaO_2. However, this did not affect the biomarkers of HIE or neurological outcome. The pathogenesis of HIE is likely to be complex, and the outcomes of CA patients can probably not be improved simply by increasing the oxygen delivery to the brain. The damaged neurons may not be able to utilize all the available oxygen efficiently, as has been shown to happen in patients with sepsis [154]. Some of the mechanisms leading to HIE are caused by ischemia-reperfusion damage and increased production of ROS rather than hypoperfusion [13], suggesting that increasing cerebral oxygenation may have its drawbacks. Although the current study did not show evidence of harm related to moderate hyperoxia, larger trials are needed before definitive conclusions regarding safe PaO_2 range during post-resuscitation care can be drawn.

Blood pressure level and HIE

As mentioned above, cerebral perfusion is decreased and the autoregulation of CBF is often impaired after CA and successful resuscitation. This means that the MAP range where cerebral autoregulation remains functional is narrowed and right-shifted [136]. The injured brain becomes vulnerable to systemic hypotension, and in order to maintain adequate cerebral perfusion, high enough MAP becomes essential. Because of the lack of high-quality data, this minimum blood pressure threshold is unknown, and the current European guidelines do not give any specific target level for MAP after CA. Instead, they recommend aiming for an adequate urine output (1 ml/kg/h) and normal or decreasing plasma lactate levels [15].

In previous observational studies, low arterial pressure during the early post-resuscitation period has been consistently associated with increased mortality and poor neurological outcome [78-91]. However, it has been unclear whether supporting the circulation with vasoactive agents could optimize cerebral perfusion and improve outcomes, or whether the patients with severe hemodynamic instability and need for high vasopressor support represent a subgroup of patients with longer pre-hospital no-flow times and therefore a worse prognosis per se. In addition, vasoactive agents and inotropes have many potential adverse effects, and in some studies, their increased use after CA has been associated with poor outcome [81 86].

The current study was the first randomised clinical trial comparing the effects of targeting two different levels of MAP on biomarkers of brain injury, brain oxygenation, epileptic activity, and neurological outcome in patients resuscitated after CA. Targeting a higher blood pressure level (MAP 80-100 mmHg) using vasoactive infusions was feasible, but it did not affect any of the pre-defined outcomes as compared with a lower blood pressure level (MAP 65-75 mmHg). These findings do not support aiming for higher blood pressure levels in comatose CA patients in an attempt to attenuate the developing brain damage. On the other hand, we did not observe any adverse effects related to the increased vasopressor load in the higher MAP group, which was in accordance with a recent high-resolution observational study of the Finnish ICUs [87].

Our results have been supported by the Neuroprotect study, another randomised clinical trial comparing MAP 85-100 mmHg with the conventional MAP 65 mmHg level in post-CA patients, published soon after the COMACARE trial [146]. The authors reported an increase of cerebral oxygenation in the higher MAP group, but in line with the current study, there was no difference in NSE or neurological outcome between the groups. Moreover, there was no difference in the diffusion weighted MRI results, which was the primary outcome of the Neuroprotect study. In contrast with the COMACARE trial, the Neuroprotect trial included patients with all initial rhythms and thus the overall proportion of patients with good neurological outcome (CPC 1-2) was significantly smaller (39% vs. 65%).

Although the results of both COMACARE and Neuroprotect studies endorse the view that additional vasopressor support to target a higher MAP level higher than the conventional 65 mmHg may not be effective in attenuating HIE, they are still far from conclusive for several reasons. First, both trials were relatively small pilot studies not powered to detect differences in outcome measures such as long-term neurological recovery or mortality. It is possible that the sample size calculation in study II was too optimistic, and the studied population was too small to detect differences in NSE as well. A larger randomised trial comparing different blood pressure levels is warranted before definitive conclusions on the benefit or harm of targeting higher MAP after OHCA can be drawn. Second, there is wide variation in the cerebrovascular haemodynamics and cerebral autoregulatory thresholds between patients, depending on the extent of the pre-hospital ischaemic insult, age, and previous hypertensive status. Thus, it might be that universal hemodynamic targets adequate for all patients cannot be found, and individual goals should be sought

instead. In some patients, the baseline brain damage might be too extensive to allow them to benefit from any intervention and on the other hand, some patients may recover well regardless of the targeted blood pressure level during ICU care. The challenge is to find the patients most likely to benefit from hemodynamic interventions and to develop a way to determine the optimal blood pressure level for each patient.

Cerebral oxygenation

Cerebral oxygenation is thought to reflect CBF, and moderate correlation between frontal rSO_2 and cerebral perfusion pressure has been found in previous studies [155]. Optimising the oxygenation and perfusion of the brain is one of the main goals of post-resuscitation care, and it has been thought that the information provided by NIRS could provide a feasible target for goal-directed therapy after CA. The promising results of frontal rSO_2 monitoring in different perioperative settings [130] and in predicting ROSC during CPR [131] have further increased the expectations regarding its usefulness with resuscitated patients. However, the significance of optimising frontal rSO_2, cerebral perfusion pressure, and CBF to improve outcomes during post-resuscitation care remains undefined.

The current study was the largest cohort of post-CA patients with continuous NIRS monitoring analysed so far. We found that in this relatively selected population of OHCA patients with shockable initial rhythms, frontal rSO_2 during the first 36 h of intensive care was not associated with NSE or neurological outcome. Our results do not support the hypothesis that the outcome of OHCA patients could be improved by goal-directed therapy targeting a specific frontal rSO_2 level, and the role of NIRS monitoring as part of the outcome prediction in resuscitated patients is questioned as well.

Our findings contradict the results of many of the previous studies investigating NIRS in resusctiated CA patients [133-135]. Interestingly, a striking difference in the overall outcome of the patients can be seen between the studies that have reported a positive association between rSO_2 and outcome, and those that have not. In the current study, 65% of patients recovered to CPC 1-2. In the two other studies where no clear association between frontal rSO_2 and outcome could be found, the overall prognosis for good outcome was 47% and 54% [132,137]. In contrast, in the studies where frontal rSO_2 predicted outcome, the proportion of patients with good neurological outcome varied between 4-38%. Thus, based on the results of these few studies with relatively small sample sizes, it seems that the ability of NIRS to predict outcome becomes poorer as the overall outcome of the study population improves. An extreme example is the Japanese study of 672 OHCA patients, where frontal rSO_2 over 42% at hospital arrival predicted good outcome with 95% specificity and 79% sensitivity, but the mean rSO_2 was only 21% and the overall proportion of patients with good neurological outcome only 4% [135]. Hence, if the prognostic accuracy of frontal rSO_2 is acceptable only in situations where poor outcome is already evident

by conventional means, it is unlikely that NIRS monitoring would prove to be a useful addition in the prognostication of CA patients.

Another problem with NIRS seems to be that even in the studies that have found an association between cerebral oxygenation and prognosis, there is significant overlap in the measured frontal rSO_2 range between patients with good and poor outcome. Because of this, clear cut-off limits have been impossible to establish. In addition, the absolute difference in frontal rSO_2 between patients with good and poor outcome has been very small in most studies, making the interpretation of frontal rSO_2 values very difficult in the clinical setting and further compromising the value of NIRS monitoring in post-resuscitation care.

In the current study, high-normal $PaCO_2$ and moderate hyperoxia after CA resulted in significantly higher rSO_2 as compared with low-normal $PaCO_2$ and normoxia, respectively. In contrast, higher blood pressure level did not have significant effect on cerebral oxygenation, suggesting that the autoregulation of CBF may remain functional even with a lower blood pressure level of 65-75 mmHg during the post-resuscitation period. This is in line with a previous small study where increasing MAP from 70 to 90 mmHg did not affect brain tissue oxygenation [156]. On the contrary, in the Neuroprotect trial, rSO_2 was significantly higher in patients assigned to the higher MAP group and this finding was further supported with significantly higher cerebral perfusion in a subset of patients in whom transcranial Doppler measurement was performed [146]. The clinical implications of these findings remain unclear so far.

In a previous study assessing CBF with serial duplex ultrasound measurements after CA, the investigators did not find any association between CBF and outcome [157], which is in accordance with our findings. However, they did find a correlation between the systemic blood pressure and CBF in patients with poor outcome, suggesting that impaired autoregulation of CBF during post-resuscitation care could be related to poor prognosis. Impaired autoregulation has been previously determined with the cerebral oximetry index (COx), which is a correlation coefficient between MAP and rSO_2 [158,159]. Impaired autoregulation, defined as COx > 0.3 during the first 24 hours after CA, has been associated with poor outcome [158]. The COx has also been used to estimate the optimal blood pressure levels for individual patients after CA and, interestingly, those levels have been significantly higher than those recommended by the current guidelines. It is possible that in the future, rSO_2 monitoring after CA will have an important role in the assessment of CBF autoregulation, but interventional studies are needed to determine whether treating the blood pressure to the optimal target predicted by COx really improves outcomes.

Blood pressure and myocardial damage

Acute coronary occlusion is the most common cause of OHCA, and the developing myocardial infarction can lead to decreased cardiac contractility and reduced CO in resuscitated patients [76]. Moreover, the global ischaemia–reperfusion injury

developing after CA and resuscitation can cause myocardial stunning and compromise normal cardiac function [73]. The reduced CO can lead to diastolic hypotension and insufficient coronary perfusion, further aggravating myocardial ischaemia and reducing CO even more. Eventually, this can result in a downward spiral, ending in multiple organ failure and cardiovascular collapse [159]. In previous studies, hypotension and even low-normal blood pressure at hospital admission have been associated with increased mortality after AMI [160]. Accordingly, the current guidelines recommend using vasopressors and inotropes to maintain systemic perfusion in patients with AMI presenting with low MAP and severe systolic dysfunction [161].

Excessive vasopressor can increase afterload and myocardial oxygen consumption, thereby aggravating the developing myocardial damage [162]. In addition, $ß_1$-stimulating agents, such as noradrenaline and dobutamine, can also increase the risk of ventricular arrhythmias and new onset CA, and the increased vasoconstriction may lead to impaired microcirculation and reduced oxygen delivery in various tissues. The optimal level of vasopressor and inotrope support that would balance coronary perfusion, afterload, myocardial oxygen consumption and arrhythmogenic risk remains unknown.

In studies II-III, the concentration of TnT was comparable in both MAP groups, suggesting that the extent of myocardial damage was comparable despite the different blood pressure levels and the significantly higher noradrenaline load in the high-normal MAP group. In contrast, in the subgroup of OHCA patients with concurrent AMI and vasopressor dependent hypotension in study V, targeting the higher MAP level of 80/85-100 mmHg was associated with a 27% reduction in myocardial damage as assessed with the area under the 72-hour TnT curve. Although cardiac troponin is not the golden standard of assessing myocardial infarct size, it has correlated well with SPECT and MRI findings in previous studies [121]. Importantly, despite the significantly higher vasopressor load in the higher MAP group, the risk for new onset ventricular arrhythmias was not increased.

The final size of the developing myocardial infarction after a coronary occlusion can only be affected by prompt restoration of adequate perfusion and oxygen delivery to the myocardium. So far, only urgent revascularisation of the culprit artery has been shown to improve the outcome of AMI patients with cardiogenic shock [163]. Our findings suggest that targeting a higher blood pressure level after coronary intervention may help to maintain sufficient perfusion in the affected myocardium and to reduce the final infarct size, providing a new therapeutic option for hypotensive AMI patients. Based on these results, it seems that the beneficial effects of vasopressors on diastolic blood pressure and coronary perfusion may be greater than their potential adverse effects on arrhythmogenic risk, afterload, and myocardial oxygen consumption.

Despite the smaller myocardial damage associated with the higher blood pressure level in patients included in study V, the mortality at 6 months was comparable between the two MAP groups. Because the cause of death was HIE in 70% of the patients included in the analysis, it seems logical that an intervention that was associated with a reduction in myocardial damage did not affect mortality in this relatively

small sample of patients. Interestingly, 7 out of 10 patients who died because of early haemodynamic shock were assigned to the lower MAP group. This supports the hypothesis that aggressive goal directed hemodynamic resuscitation immediately after successful coronary revascularisation may help prevent the deathly spiral of cardiogenic shock described above. However, larger randomised trials are needed before definitive conclusions on the possible benefits of this strategy on long term outcomes can be made.

Limitations

Several limitations in the current study should be addressed. First, despite we conducted a multicentre trial, most included patients (69%) were recruited at Helsinki University Hospital. Second, although interventions aiming at affecting the course of HIE should be started as early as possible, the study interventions were started at the hospital after ICU admission and not during pre-hospital care. However, the delay between ROSC and the beginning of the interventions was reasonably short for most participants. Also, the strict control of $PaCO_2$, PaO_2, and MAP levels in the pre-hospital setting would have been challenging especially in areas where a pre-hospital physician is not available. Third, as $PaCO_2$, PaO_2, $EtCO_2$, SpO_2, and arterial pressure are routinely monitored variables in the ICU, and the ICU staff was needed in targeting the designated $PaCO_2$, PaO_2 and MAP level, the study interventions could not be blinded. However, the neurologist assessing the 6-month neurological outcome and the neurophysiologist analysing the EEGs were blinded from the study group allocations.

Fourth, the small sample size, particularly the small number of patients with poor outcome, limits the strength of conclusions that can be drawn. The study was not powered to detect differences in mortality or neurological outcome. Thus, it is possible that some benefit or harm of the studied interventions remained undetected and no definitive conclusions regarding their efficacy or safety can be drawn. Fifth, the overall outcome in these studies was exceptionally good for an OHCA cohort. It should be emphasised that the studied population was positively selected regarding age, initial rhythm, and a presumed cardiac cause of the arrest, limiting the generalisability of the results. Sixth, we used a four-channel technique for EEG monitoring. There is a risk that some focal epileptic activity may have been unnoticed. Seventh, the NIRS probes attached on the patients' forehead provided information only about a small area of the frontal cerebral cortex, leaving other parts of the brain uncovered. Some bias could have been caused to the results because of regional variation in rSO_2.

Eighth, we chose the NSE concentration at 48 h as the primary outcome of the current study because it has been well documented as a surrogate marker of HIE and it has an established role in the multimodal prognostication of the OHCA patients [116]. A major pitfall of NSE is that it is not entirely specific to neurons and substantial amounts of the enzyme is also found in erythrocytes. Thus, even mild haemolysis

can increase the NSE concentration in the blood and cause bias to the results [114]. In the current study, 463 serum samples were obtained all together for the NSE analyses. In all samples taken in the Finnish centres (n = 437), haemolysis was assessed using the Roche haemolysis index. In seven samples (1.5%), the haemolysis index was over 50, corresponding to more than 500 mg of free Hb per litre, and these samples were excluded from the analyses. This same threshold has been used in previous studies [109]. In the samples taken at the Danish centre (n = 26), the NSE concentration was analysed immediately using the same kits as in the Finnish laboratory, but haemolysis was not assessed. In the remaining 430 samples, there was detectable haemolysis (haemolysis index ≥ 10) in 150 samples (34.9%). The mean ± SD haemolysis index in these samples was 19.0 ± 9. The amount of the moderately haemolytic samples was comparable in all the intervention groups and the main findings of the study remained unchanged even when all samples with detectable haemolysis were excluded from the analyses.

Regarding study IV, the design was conceived post hoc and it was not included in the original study protocol. In addition, the study was based on measurements of rSO_2, which is a surrogate indicator of CBF. Assessment of transcranial Doppler ultrasound, a direct measurement of blood flow in cerebral arteries, could have provided additional information.

Regarding study V, we used TnT to assess myocardial infarct size although MRI is the current golden standard. Cardiac MRI was not part of the original protocols of the COMACARE or Neuroprotect studies, and for practical reasons, it would have been difficult to implement for intubated and mechanically ventilated patients. Moreover, MRI would not have been feasible nor safe for the patients with the largest infarcts and haemodynamic shock, and some of these patients would have died before the MRI, causing bias to the results. Although the area under the 72-hour TnT curve has correlated well with the infarct size assessed with MRI or PET in previous studies [121,122], TnT is still a surrogate marker of myocardial damage and there are factors that can affect its level regardless of cardiac ischaemia. For example, renal insufficiency or chest compressions during CPR can be the reason for elevated TnT levels in resuscitated patients without AMI [124,126], and both of these factors are potential sources of bias in our results. Nevertheless, baseline TnT levels and daily creatinine values during the 72-hour study period were well balanced between the groups.

In addition, the universal definitions for AMI had to be adapted in study V. Because the patients had to be unconscious for inclusion, chest pain could not be assessed. Moreover, because virtually all resuscitated patients have some form of ECG abnormalities and rise of the troponins, these criteria could not be used either. Similarly, previous shock definitions for cardiogenic shock include signs of end-organ hypoperfusion such as altered mental status, cold skin, increased lactate level and decreased urine output that are not applicable in intubated post-CA patients with hypothermia induced cold diuresis and consistently elevated lactate levels upon admission. However, we feel that the definitions for AMI and vasopressor dependent hypotension used in this study provided the most robust data possible in

this setting. Also, routine echocardiographic assessment was not performed for all patients. This could have provided additional information about myocardial contractility and CO in the different MAP groups. Additionally, the intervention protocol to target the designated MAP level was slightly different between the COMACARE and Neuroprotect studies. However, the TnT levels were very consistent across both trials, suggesting that the observed difference in the extent of myocardial damage was more related to the MAP target than to the combination of the drugs used. Finally, because the design of study V was conceived post hoc, its results should be interpreted as hypothesis generating and further confirmed or refuted by future trials.

Summary and conclusions

The present study investigated the feasibility of targeting different $PaCO_2$, PaO_2, and MAP levels in comatose OHCA patients after successful resuscitation; the effect of these interventions on the extent of the developing neurological and myocardial damage, cerebral oxygenation, and epileptic activity; and the association between cerebral oxygenation and the extent of the developing neurological damage. Following conclusions can be drawn:

1. Targeting low-normal or high-normal $PaCO_2$, normoxia or moderate hyperoxia, and low-normal or high-normal MAP is feasible in comatose patients after OHCA. With frequent ABG analyses and adjustments of MV on the ventilator, $PaCO_2$ can be kept within a very narrow range as targeted, and the oxygenation of blood can be regulated with adjustments on FiO_2 and PEEP level. Hypotension can be corrected, and MAP level can be accurately controlled with a continuous infusion of noradrenaline without significant adverse effects. Based on these results, conducting a full-scale randomised trial investigating the effect of different $PaCO_2$, PaO_2, and MAP levels after CA seems feasible.

2. Targeting high-normal $PaCO_2$, moderate hyperoxia, or high normal MAP after resuscitation from OHCA had no effect on the investigated markers of brain injury or epileptic activity, as compared with targeting low-normal $PaCO_2$, normoxia, and low-normal MAP, respectively. Higher $PaCO_2$ and moderate hyperoxia increased cerebral oxygenation but MAP level did not affect it. Because of the pilot nature and small sample size of the study, definitive conclusions regarding the efficacy or safety of these interventions cannot be drawn.

   In OHCA patients with concurrent AMI and hypotension, higher MAP level was associated with smaller myocardial injury. Due to the small sample size and the post hoc design of the analysis, this result should be interpreted with caution and seen as hypothesis generating. Further studies are needed to ascertain the effect of MAP level on the developing myocardial injury in AMI patients.

3. Cerebral oxygenation was not associated with the severity of neurological damage or neurological outcome. This finding questions the benefit of routine NIRS-monitoring in resuscitated patients.

Future perspectives

The neutral findings between low-normal and high-normal $PaCO_2$ in the current study do not encourage performing a larger trial with the same $PaCO_2$ targets in the future. However, more information about the possible neuroprotective effects of hypercapnia is needed. A large randomised trial (Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest [TAME], NCT03114033) comparing mild hypercapnia (6.7-7.3 kPa) with normocapnia has already been initiated, and hopefully it will provide some answers on this matter in the near future. Future research should focus on further elucidating the neuroprotective mechanisms of CO_2, and defining the optimal target level of $PaCO_2$ that would balance the benefits and the known adverse effects of increased ICP, acidosis and myocardial impairment.

What comes to oxygen, the findings of the current study support the view that moderate hyperoxia is not harmful for OHCA patients. However, the possible beneficial or detrimental effects of the increased oxygen delivery on the recovering brain and patient outcomes remain unclear. There is a great need for large clinical trials studying the long-term effects of different oxygen targets in CA patients, and the results of the current study support the feasibility and safety of such a trial. The results of the Reduction of Oxygen After Cardiac Arrest (EXACT, NCT03138005) trial comparing SpO_2 98-100% target with SpO_2 90-94% target after OHCA will provide some insight to this matter in the future. Unfortunately, the interventions of the EXACT trial are limited to the pre-hospital phase only, and new trials extending the intervention time to the first days of intensive care are required to define the optimal PaO_2 target after OHCA.

The current study was the first randomised trial assessing the effects of different blood pressure targets in resuscitated patients. Unfortunately, the small sample size limits the strength of conclusions that can be made, and larger trials powered to detect differences in mortality and long-term neurological outcome are needed to better understand the effects of different MAP levels after OHCA. The optimal blood pressure level is likely to be different between patients, depending on their background and baseline comorbidities. Thus, instead of applying a 'one-size-fits-all' haemodynamic strategy for everyone, future research should focus on bedside assessment of CBF autoregulation and finding personalised perfusion targets for each patient.

As for NIRS, our results do not support the hypothesis that the outcome of OHCA patients could be improved by targeting a specific frontal rSO_2 level during the post-resuscitation care. In addition, our results do not support using NIRS monitoring as part of the multi-modal outcome prediction after CA, questioning the role of routine NIRS monitoring in these patients. However, NIRS may have an

important role in the assessment of autoregulation of CBF and in defining individual blood pressure targets for different patients. Additional analyses of the current trial focusing on this matter have already been started [164], and more studies should be planned in the future. An interesting approach to the individual blood pressure targets would be to predict the optimal blood pressure for each patient using NIRS and the COx, and to randomise patients to hourly optimised versus conventional blood pressure targets accordingly. Unfortunately, this kind of trial would be technically challenging and might prove to be too complicated to put into practice in most ICUs, limiting the size of the study.

As mentioned before, interventions aiming at attenuating the developing brain injury after OHCA should be started as early as possible. In the current study, the designated $PaCO_2$, PaO_2, and MAP levels were targeted immediately after ICU admission, but even this may be too late as the delay from ROSC to hospital can sometimes be hours. Optimising ventilatory targets and haemodynamic support already in the field could be pivotal in preventing the developing cascade of cerebral vasoconstriction, hypoxia, and HIE during the first hours after ROSC. Targeting a specific narrow range of $PaCO_2$, PaO_2, and MAP in the pre-hospital setting is challenging, however, and would require a physician with the equipment for ABG analysis on-site. In Finland, this is currently possible around the major cities with an EMS doctor unit available within a relatively short distance. In these areas, a small pilot study comparing the timing of the interventions (immediately after ROSC vs. ICU admission) should be feasible and could show the way for larger trials in the future.

The results of study V justify a larger randomised clinical trial to define the optimal dosage of pharmacological support in AMI patients with vasopressor dependent hypotension and with or without preceding CA. In addition to myocardial damage, this new trial should also assess differences in coronary perfusion and cardiac metabolites.

In addition to defining the optimal $PaCO_2$, PaO_2, and MAP targets, there are several other post-ROSC interventions that need further investigation in the near future. For example, the role of routine coronary angiography in improving outcomes after OHCA should be defined. Moreover, the effects of xenon on mortality and neurological outcome should be assessed in an adequately powered randomised trial. The control of seizures with antiepileptic drugs is another pressing topic in the field of post-resuscitation care. Finally, future studies should focus on finding new, more accurate biomarkers for the prognostication of resuscitated patients. Fortunately, some potential candidates have already been introduced, neurofilament light chain seeming to be the most promising of these so far [165].

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References

1. Berdowski J, Berg RA, Tijssen JGP, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation. 2010; 81(11):1479-1487.
2. Hiltunen P, Kuisma M, Silfvast T, et al. Regional variation and outcome of out-of-hospital cardiac arrest (ohca) in Finland – the Finnresusci study. Scand J Trauma Resusc Emerg Med. 2012; 20(80):1-8.
3. Tiainen M, Vaahersalo J, Skrifvars MB, et al. Surviving out-of-hospital cardiac arrest - The neurological and functional outcome and health-related quality of life one year later. Resuscitation. 2018; 129:19-23.
4. Eng Hock Ong M, Perkins GD, Cariou A. Out-of-hospital cardiac arrest: prehospital management. The Lancet. 2018; 391(10124):980-988.
5. Hassager C, Nagao K, Hildick-Smith D. Out-of-hospital cardiac arrest: in-hospital intervention strategies. The Lancet. 2018; 391(10124):989-998.
6. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002; 346(8):557-563.
7. The hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002; 346(8):549-556.
8. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. N Engl J Med. 2013; 369(23):2197-2206.
9. Laitio R, Hynninen M, Arola O, et al. Effect of Inhaled Xenon on Cerebral White Matter Damage in Comatose Survivors of Out-of-Hospital Cardiac Arrest. JAMA. 2016; 315(11):1120-1129.
10. Arola O, Saraste A, Laitio R, et al. Inhaled Xenon Attenuates Myocardial Damage in Comatose Survivors of Out-of-Hospital Cardiac Arrest. J Am Coll Cardiol. 2017; 70(21):2652-2660.
11. Jeong J, Ro YS, Do Shin S, et al. Association of time from arrest to percutaneous coronary intervention with survival outcomes after out-of-hospital cardiac arrest. Resuscitation. 2017; 115:148-154.
12. Lemiale V, Dumas F, Mongardon N, et al. Intensive care unit mortality after

cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013; 39(11):1972-1980.

13. Llitjos J-F, Mira J-P, Duranteau J, et al. Hyperoxia toxicity after cardiac arrest: What is the evidence? Ann Intensive Care. 2016; 6(1):1-9.

14. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. Stroke. 1997; 28(8):1569-1573.

15. Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015: Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015. Resuscitation. 2015; 95:202-222.

16. Myat A, Song K-J, Rea T. Out-of-hospital cardiac arrest: current concepts. The Lancet. 2018; 391(10124):970-979.

17. Spaulding C, Joly L-M, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997; 336(23):1629-1633.

18. Davies M, Thomas A. Thrombosis and acute coronary-artery lesions in sudden cardiac ischemic death. N Engl J Med. 1984; 310(18):1137-1140.

19. Engdahl J, Holmberg M, Karlson BW, et al. The epidemiology of out-of-hospital "sudden" cardiac arrest. Resuscitation. 2002; 52:235-245.

20. Perkins GD, Handley AJ, Koster RW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. Resuscitation. 2015; 95:81-99.

21. Saarinen S, Salo A, Boyd J, et al. Factors determining level of hospital care and its association with outcome after resuscitation from pre-hospital pulseless electrical activity. Scand J Trauma Resusc Emerg Med. 2018; 26(1):1-9.

22. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: Carbon dioxide. Critical Care. 2010; 14(220):1-7.

23. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. J Physiol (Lond). 2011; 589:3039-3048.

24. Sundgreen C, Larsen FS, Herzog TM, et al. Autoregulation of Cerebral Blood Flow in Patients Resuscitated From Cardiac Arrest. Stroke. 2000; 32:128-132.

25. Kavanagh BP, Hedenstierna G. Respiratory Physiology and Pathophysiology. In: Gropper MA, Miller RD. Miller's Anesthesia. 9th ed. 2020; 354-383.

26. Shoja MM, Tubbs RS, Shokouhi G, et al. The potential role of carbon dioxide in the neuroimmunoendocrine changes following cerebral ischemia. Life Sciences. 2008; 83:381-387.

27. Tolner EA, Hochman DW, Hassinen P, et al. Five percent CO2 is a potent,

fast-acting inhalation anticonvulsant. Epilepsia. 2010; 52(1):104-114.

28. Zhou Q, Cao B, Niu L, et al. Effects of Permissive Hypercapnia on Transient Global Cerebral Ischemia-Reperfusion Injury in Rats. Anesthesiology. 2010; 112(2):288-297.

29. Babini G, Ristagno G, Boccardo A, et al. Effect of mild hypercapnia on outcome and histological injury in a porcine post cardiac arrest model. Resuscitation. 2019; 135:110-117.

30. Ganga HV, Kallur KR, Patel NB, et al. The impact of severe acidemia on neurologic outcome of cardiac arrest survivors undergoing therapeutic hypothermia. Resuscitation. 2013; 84(12):1723-1727.

31. Mekontso Dessap A, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. Intensive Care Med. 2009; 35(11):1850-1858.

32. Schneider AG, Eastwood GM, Bellomo R, et al. Arterial carbon dioxide tension and outcome in patients admitted to the intensive care unit after cardiac arrest. Resuscitation. 2013; 84(7):927-934.

33. Vaahersalo J, Bendel S, Reinikainen M, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med. 2014; 42(6):1463-1470.

34. Eastwood GM, Schneider AG, Suzuki S, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: A phase II multi-centre randomised controlled trial (the CCC trial). Resuscitation. 2016; 104:83-90.

35. Kilgannon JH, Hunter BR, Puskarich MA, et al. Partial pressure of arterial carbon dioxide after resuscitation from cardiac arrest and neurological outcome: A prospective multi-center protocol-directed cohort study. Resuscitation. 2019; 135:212-220.

36. Roberts BW, Kilgannon JH, Chansky ME, et al. Association between post-resuscitation partial pressure of arterial carbon dioxide and neurological outcome in patients with post-cardiac arrest syndrome. Circulation. 2013; 127(21):2107-2113.

37. Roberts BW, Kilgannon JH, Chansky ME, et al. Association between initial prescribed minute ventilation and post-resuscitation partial pressure of arterial carbon dioxide in patients with post-cardiac arrest syndrome. Ann Intensive Care. 2014; 4(9):1-9.

38. Helmerhorst HJF, Roos-Blom M-J, van Westerloo DJ, et al. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Critical Care. 2015; 19(1):348.

39. Wang C-H, Huang C-H, Chang W-T, et al. Association between early arterial

blood gas tensions and neurological outcome in adult patients following in-hospital cardiac arrest. Resuscitation. 2015; 89:1-7.

40. McKenzie N, Williams TA, Tohira H, et al. A systematic review and meta-analysis of the association between arterial carbon dioxide tension and outcomes after cardiac arrest. Resuscitation. 2017; 111:116-126.

41. Tolins ML, Henning DJ, Gaieski DF, et al. Initial arterial carbon dioxide tension is associated with neurological outcome after resuscitation from cardiac arrest. Resuscitation. 2017; 114:53-58.

42. Wang HE, Prince DK, Drennan IR, et al. Post-resuscitation arterial oxygen and carbon dioxide and outcomes after out-of-hospital cardiac arrest. Resuscitation. 2017; 120:113-118.

43. Moon S-W, Lee S-W, Choi S-H, et al. Arterial minus end-tidal CO2 as a prognostic factor of hospital survival in patients resuscitated from cardiac arrest. Resuscitation. 2007; 72(2):219-225.

44. Lee BK, Jeung KW, Lee HY, et al. Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia. Am J Emerg Med. 2014; 32(1):55-60.

45. Eastwood GM, Suzuki S, Lluch C, et al. A pilot assessment of alpha-stat vs pH-stat arterial blood gas analysis after cardiac arrest. Journal of Critical Care. 2015; 30(1):138-144.

46. Ebner F, Harmon MBA, Åneman A, et al. Carbon dioxide dynamics in relation to neurological outcome in resuscitated out- of-hospital cardiac arrest patients: an exploratory Target Temperature Management Trial substudy. Critical Care. 2018; 22(1):1-10.

47. Pitcher JH, Dziodzio J, Keller J, et al. Hemodynamic, Biochemical, and Ventilatory Parameters are Independently Associated with Outcome after Cardiac Arrest. Neurocritical Care. 2018; 135(10):1-8.

48. Spindelboeck W, Schindler O, Moser A, et al. Increasing arterial oxygen partial pressure during cardiopulmonary resuscitation is associated with improved rates of hospital admission. Resuscitation. 2013; 84(6):770-775.

49. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. Resuscitation. 2015; 95:100-147.

50. Liu Y, Rosenthal RE, Haywood Y, et al. Normoxic Ventilation After Cardiac Arrest Reduces Oxidation of Brain Lipids and Improves Neurological Outcome. Stroke. 1998; 29:1679-1686.

51. Pilcher J, Weatherall M, Shirtcliffe P, et al. The effect of hyperoxia following cardiac arrest – A systematic review and meta-analysis of animal trials. Resuscitation. 2012; 83(4):417-422.

52. Kuisma M, Boyd J, Voipio V, et al. Comparison of 30 and the 100% inspired oxygen concentrations during early post-resuscitation period: a randomised controlled pilot study. Resuscitation. 2006; 69(2):199-206.

53. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010; 303(21):2165-2171.

54. Kilgannon JH, Jones AE, Parrillo JE, et al. Relationship Between Supranormal Oxygen Tension and Outcome After Resuscitation from Cardiac Arrest. Circulation. 2011; 123(23):2717-2722.

55. Bellomo R, Bailey M, Eastwood GM, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Critical Care. 2011; 15(2):R90.

56. Janz DR, Hollenbeck RD, Pollock JS, et al. Hyperoxia is associated with increased mortality in patients treated with mild therapeutic hypothermia after sudden cardiac arrest. Crit Care Med. 2012; 40(12):3135-3139.

57. Elmer J, Scutella M, Pullalarevu R, et al. The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med. 2015; 41(1):49-57.

58. Roberts BW, Kilgannon JH, Hunter BR, et al. Association Between Early Hyperoxia Exposure After Resuscitation from Cardiac Arrest and Neurological Disability. Circulation. 2018; 137(20):2114-2124.

59. Ihle JF, Bernard S, Bailey MJ, et al. Hyperoxia in the intensive care unit and outcome after out-of-hospital ventricular fibrillation cardiac arrest. Crit Care Resusc. 2013; 15(3):186-190.

60. Nelskylä A, Parr M, Skrifvars MB. Prevalence and factors correlating with hyperoxia exposure following cardiac arrest – an observational single centre study. Scand J Trauma Resusc Emerg Med. 2013; 20(1):80-87.

61. Oh YT, Kim YH, Sohn YD, et al. Early hyperoxemia may not increase mortality after cardiac arrest: a pilot study. Clin Exp Emerg Med. 2014; 1(1):28-34.

62. Auenmueller von KI, Christ M, Sasko BM, Trappe H-J. The Value of Arterial Blood Gas Parameters for Prediction of Mortality in Survivors of Out-of-hospital Cardiac Arrest. Journal of Emergencies, Trauma, and Shock. 2017; 10(3):134-139.

63. Ebner F, Ullén S, Åneman A, et al. Associations between partial pressure of oxygen and neurological outcome in out-of-hospital cardiac arrest patients: an explorative analysis of a randomized trial. Critical Care. 2019; 23(1):1-11.

64. Wang C-H, Chang W-T, Huang C-H, et al. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. Resuscitation. 2014; 85(9):1142-1148.

65. Helmerhorst HJF, Roos-Blom M-J, van Westerloo DJ, et al. Association Between Arterial Hyperoxia and Outcome in Subsets of Critical Illness. Crit Care Med. 2015; 43(7):1508-1519.

66. Patel JK, Kataya A, Parikh PB. Association between intra- and post-arrest hyperoxia on mortality in adults with cardiac arrest – A systematic review and meta-analysis. Resuscitation. 2018; 127:83-88.

67. The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. N Engl J Med. 2020; 382:989-998.

68. Baird G. Preanalytical considerations in blood gas analysis. Biochem Med. 2013; 23(1):19-27.

69. Bisson J, Younker J. Correcting arterial blood gases for temperature: (when) is it clinically significant? Nursing in Critical Care. 2006; 11:232-238.

70. Bacher A. Effects of body temperature on blood gases. In: Pinsky MR. Applied Physiology in Intensive Care Medicine 1. 3rd ed. 2012; 55-58.

71. Docherty A, Emelifeonwu J, Andrews P. Hypothermia after traumatic brain injury. JAMA. 2018; 320(21):2204-2206.

72. Pynnönen L, Falkenbach P, Kämäräinen A, et al. Therapeutic hypothermia after cardiac arrest: cerebral perfusion and metabolism during upper and lower threshold normocapnia. Resuscitation. 2011; 82(9):1174-1179.

73. Laurent I, Monchi M, Chiche J-D, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol. 2002; 40(12):2110-2116.

74. Adrie C, Adib-Conquy M, Laurent I, et al. Successful Cardiopulmonary Resuscitation After Cardiac Arrest as a "Sepsis-Like" Syndrome. Circulation. 2002; 106(5):562-568.

75. Miller JB, Donnino MW, Rogan M, et al. Relative adrenal insufficiency in post-cardiac arrest shock is under-recognized. Resuscitation. 2008; 76(2):221-225.

76. Dumas F, Cariou A, Manzo-Silberman S, et al. Immediate Percutaneous Coronary Intervention Is Associated with Better Survival After Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Interv. 2010; 3(3):200-207.

77. Hachimi-Idrissi S, Corne L, Huyghens L. The effect of mild hypothermia and induced hypertension on long term survival rate and neurological outcome after asphyxial cardiac arrest in rats. Resuscitation. 2001; 49:73-82.

78. Kilgannon JH, Roberts BW, Reihl LR, et al. Early arterial hypotension is common in the post-cardiac arrest syndrome and associated with increased in-hospital mortality. Resuscitation. 2008; 79(3):410-416.

79. Trzeciak S, Jones AE, Kilgannon JH, et al. Significance of arterial hypotension after resuscitation from cardiac arrest. Crit Care Med. 2009; 37(11):2895-2903.

80. Kaji AH, Hanif AM, Thomas JL, et al. Out-of-hospital cardiac arrest: Early in-hospital hypotension versus out-of-hospital factors in predicting in-hospital mortality among those surviving to hospital admission. Resuscitation. 2011; 82(10):1314-1317.

81. Beylin ME, Perman SM, Abella BS, et al. Higher mean arterial pressure with or without vasoactive agents is associated with increased survival and better neurological outcomes in comatose survivors of cardiac arrest. Intensive Care Med. 2013; 39(11):1981-1988.

82. Kim HC, Yoo J-W, Lim SY, et al. Mortality after in-hospital cardiopulmonary resuscitation: Multicenter analysis in Korea. Journal of Critical Care. 2013; 28(6):942-946.

83. Bray JE, Bernard S, Cantwell K, et al. The association between systolic blood pressure on arrival at hospital and outcome in adults surviving from out-of-hospital cardiac arrests of presumed cardiac aetiology. Resuscitation. 2014; 85(4):509-515.

84. Kilgannon JH, Roberts BW, Jones AE, et al. Arterial blood pressure and neurologic outcome after resuscitation from cardiac arrest. Crit Care Med. 2014; 42(9):2083-2091.

85. Ameloot K, Meex I, Genbrugge C, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study. Resuscitation. 2015; 91:56-62.

86. Bro-Jeppesen J, Annborn M, Hassager C, et al. Hemodynamics and Vasopressor Support During Targeted Temperature Management at 33°C Versus 36°C After Out-of-Hospital Cardiac Arrest. Crit Care Med. 2015; 43(2):318-327.

87. Laurikkala J, Wilkman E, Pettilä V, et al. Mean arterial pressure and vasopressor load after out-of-hospital cardiac arrest: Associations with one-year neurologic outcome. Resuscitation. 2016; 105:116-122.

88. Russo JJ, James TE, Hibbert B, et al. Impact of mean arterial pressure on clinical outcomes in comatose survivors of out-of-hospital cardiac arrest: Insights from the University of Ottawa Heart Institute Regional Cardiac Arrest Registry (CAPITAL-CARe). Resuscitation. 2017; 113:27-32.

89. Chiu YK, Lui CT, Tsui KL. Impact of hypotension after return of spontaneous circulation on survival in patients of out-of-hospital cardiac arrest. American Journal of Emergency Medicine. 2018; 36(1):79-83.

90. Roberts BW, Kilgannon JH, Hunter BR, et al. Association Between Elevated Mean Arterial Blood Pressure and Neurologic Outcome After Resuscitation

from Cardiac Arrest. Crit Care Med. 2018; 43(1):93-100.

91. Russo JJ, Pietro Di Santo, Simard T, et al. Optimal mean arterial pressure in comatose survivors of out-of-hospital cardiac arrest – An analysis of area below blood pressure thresholds. Resuscitation. 2018; 128:175-180.

92. Young MN, Hollenbeck RD, Pollock JS, et al. Higher achieved mean arterial pressure during therapeutic hypothermia is not associated with neurologically intact survival following cardiac arrest. Resuscitation. 2015; 88:158-164.

93. Bhate TD, McDonald B, Sekhon MS, et al. Association between blood pressure and outcomes in patients after cardiac arrest: A systematic review. Resuscitation. 2015; 97:1-6.

94. Schroeder B, Mark J, Barbeito A. Cardiovascular Monitoring. In: Gropper MA, Miller RD. Miller's Anesthesia. 9th ed. 2020; 1145-1193.

95. Slutsky AS. Mechanical Ventilation. ACCP Consensus Conference. Chest. 1993; 104(6):1833-1859.

96. Marini JJ. Evolving concepts for safer ventilation. Critical Care. 2019; 23:1301-1307.

97. Madden LK, Hill M, May TL, et al. The Implementation of Targeted Temperature Management: An Evidence-Based Guideline from the Neurocritical Care Society. Neurocritical Care. 2017; 27(3):468-487.

98. Falkenbach P, Kämäräinen A, Mäkelä A, et al. Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation. 2009; 80(9):990-993.

99. Eastwood G, Bellomo R, Bailey M, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. Intensive Care Med. 2011; 38(1):91-98.

100. Suzuki S, Eastwood GM, Glassford NJ, et al. Conservative Oxygen Therapy in Mechanically Ventilated Patients. Crit Care Med. 2014; 42(6):1414-1422.

101. Eastwood GM, Tanaka A, Espinoza EDV, et al. Conservative oxygen therapy in mechanically ventilated patients following cardiac arrest: A retrospective nested cohort study. Resuscitation. 2016; 101:108-114.

102. Finfer SR, Vincent J-L, De Backer D. Circulatory Shock. N Engl J Med. 2013; 369(18):1726-1734.

103. Angus DC, van der Poll T. Severe Sepsis and Septic Shock. N Engl J Med. 2013; 369(9):840-851.

104. Levy B, Clere-Jehl R, Legras A, et al. Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction. J Am Coll Cardiol. 2018; 72(2):173-182.

105. Grand J, Lilja G, Kjaergaard J, et al. Arterial blood pressure during targeted temperature management after out-of-hospital cardiac arrest and association

with brain injury and long-term cognitive function. European Heart Journal: Acute Cardiovascular Care. 2019; 30:1-9

106. Schmechel D, Marangos P, Zis A, et al. Brain endolases as specific markers of neuronal and glial cells. Science. 1978; 199(4326):313-315.

107. Fogel W, Krieger D, Veith M, et al. Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. Crit Care Med. 1997; 25(7):1133-1138.

108. Martens P, Raabe A, Johnsson P. Serum S-100 and Neuron-Specific Enolase for Prediction of Regaining Consciousness After Global Cerebral Ischemia. Stroke. 1998; 29:2363-2366.

109. Stammet P, Collignon O, Hassager C, et al. Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33°C and 36°C. J Am Coll Cardiol. 2015; 65(19):2104-2114.

110. Streitberger KJ, Leithner C, Wattenberg M, et al. Neuron-Specific Enolase Predicts Poor Outcome After Cardiac Arrest and Targeted Temperature Management. Crit Care Med. 2017; 45(7):1145-1151.

111. Wihersaari L, Tiainen M, Skrifvars MB, et al. Usefulness of neuron specific enolase in prognostication after cardiac arrest: Impact of age and time to ROSC. Resuscitation. 2019; 139:214-221.

112. Shinozaki K, Shigeto O, Sadahito T, et al. S-100B and neuron-specific enolase as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation: a systematic review. Critical Care. 2009; 13:R121.

113. Mjønes P, Sagatun L, Nordrum IS, et al. Neuron-Specific Enolase as an Immunohistochemical Marker Is Better Than Its Reputation. J Histochem Cytochem. 2017; 65(12):687-703.

114. Ramont L, Thoannes H, Volondat A, et al. Effects of hemolysis and storage condition on neuron-specific enolase (NSE) in cerebrospinal fluid and serum: implications in clinical practice. Clin Chem Lab Med. 2005; 43(11):1215-1217.

115. Mlynash M, Buckwalter MS, Okada A, et al. Serum Neuron-Specific Enolase Levels from the Same Patients Differ Between Laboratories: Assessment of a Prospective Post-cardiac Arrest Cohort. Neurocritical Care. 2013; 19(2):161-166.

116. Sandroni C, D'Arrigo S, Nolan JP. Prognostication after cardiac arrest. Critical Care. 2018; 22(1):150.

117. Tiainen M, Roine RO, Pettilä V,et al. Serum Neuron-Specific Enolase and S-100B Protein in Cardiac Arrest Patients Treated with Hypothermia. Stroke. 2003; 34(12):2881-2886.

118. Wang C-H, Chang W-T, Su K-I, et al. Neuroprognostic accuracy of blood

biomarkers for post-cardiac arrest patients: A systematic review and meta-analysis. Resuscitation. 2020; 148:108-117.

119. Omland T. New features of troponin testing in different clinical settings. Journal of Internal Medicine. 2010; 268(3):207-217.

120. Thygesen K, Alpert JS, Jaffe AS, et al. ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction. Circulation. 2012; 126:2020-2035.

121. Chia S, Senatore F, Raffel OC, et al. Utility of Cardiac Biomarkers in Predicting Infarct Size, Left Ventricular Function, and Clinical Outcome After Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. JACC: Cardiovascular Interventions. 2008 ;1(4):415-423.

122. 122. Nguyen TL, Phan JAK, Hee L, et al. High-sensitivity troponin T predicts infarct scar characteristics and adverse left ventricular function by cardiac magnetic resonance imaging early after reperfused acute myocardial infarction. American Heart Journal. 2015; 170(4):715-725.

123. Wong JA, Goodman SG, Yan RT, et al. Temporal management patterns and outcomes of non-ST elevation acute coronary syndromes in patients with kidney dysfunction. European Heart Journal. 2009; 30(5):549-557.

124. Kraus D, Jeinsen von B, Tzikas S, et al. Cardiac Troponins for the Diagnosis of Acute Myocardial Infarction in Chronic Kidney Disease. J Am Heart Assoc. 2018; 7(19):1-24.

125. Røsjø H, Vaahersalo J, Hagve T-A, et al. Prognostic value of high-sensitivity troponin T levels in patients with ventricular arrhythmias and out-of-hospital cardiac arrest: data from the prospective FINNRESUSCI study. Critical Care. 2014; 18(6):605.

126. Gilje P, Koul S, Thomsen JH, et al. High-sensitivity troponin-T as a prognostic marker after out-of-hospital cardiac arrest – A targeted temperature management (TTM) trial substudy. Resuscitation. 2016; 107:156-161.

127. Murkin JM, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. Br J Anaesth. 2009; 103:i3-i13.

128. Green DW, Kunst G. Cerebral oximetry and its role in adult cardiac, non-cardiac surgery and resuscitation from cardiac arrest. Anaesthesia. 2017; 72:48-57.

129. Back T, Hemmen T, Schüler OG. Lesion evolution in cerebral ischemia. Journal of Neurology. 2004; 251(4):388-397.

130. Moerman A, De Hert S. Cerebral oximetry. Current Opinion in Anaesthesiology. 2015; 28(6):703-709.

131. Schnaubelt S, Sulzgruber P, Menger J, et al. Regional cerebral oxygen saturation during cardiopulmonary resuscitation as a predictor of return of spontaneous circulation and favourable neurological outcome – A review of

the current literature. Resuscitation. 2018; 125:39-47.

132. Meex I, Dens J, Jans F, et al. Cerebral tissue oxygen saturation during therapeutic hypothermia in post-cardiac arrest patients. Resuscitation. 2013; 84(6):788-793.

133. Ahn A, Yang J, Inigo-Santiago L, Parnia S. A feasibility study of cerebral oximetry monitoring during the post-resuscitation period in comatose patients following cardiac arrest. Resuscitation. 2014; 85(4):522-526.

134. Storm C, Leithner C, Krannich A, et al. Regional cerebral oxygen saturation after cardiac arrest in 60 patients—A prospective outcome study. Resuscitation. 2014; 85(8):1037-1041.

135. Ito N, Nishiyama K, Callaway CW, et al. Noninvasive regional cerebral oxygen saturation for neurological prognostication of patients with out-of-hospital cardiac arrest: A prospective multicenter observational study. Resuscitation. 2014; 85(6):778-784.

136. Bouglé A, Daviaud F, Bougouin W, et al. Determinants and significance of cerebral oximetry after cardiac arrest: A prospective cohort study. Resuscitation. 2016; 99:1-6.

137. Genbrugge C, Eertmans W, Meex I, et al. What is the value of regional cerebral saturation in post-cardiac arrest patients? A prospective observational study. Critical Care. 2016; 20(1):1-9.

138. Hirsch LJ, La Roche SM, Gaspard N, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. Journal of Clinical Neurophysiology. 2013; 30(1):1-27.

139. Westhall E, Rossetti AO, van Rootselaar A-F, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology. 2016; 86(16):1482-1490.

140. Sondag L, Ruijter BJ, Tjepkema-Cloostermans MC, et al. Early EEG for outcome prediction of postanoxic coma: prospective cohort study with cost-minimization analysis. Critical Care. 2017; 21(1):111.

141. Scarpino M, Lolli F, Lanzo G, et al. Neurophysiology and neuroimaging accurately predict poor neurological outcome within 24 hours after cardiac arrest: The ProNeCA prospective multicentre prognostication study. Resuscitation. 2019; 143:115-123.

142. Moore CG, Carter RE, Nietert PJ, et al. Recommendations for Planning Pilot Studies in Clinical and Translational Research. Clinical and Translational Science. 2011; 4(5):332-337.

143. Arnold DM, Burns KEA, Adhikari NKJ, et al. The design and interpretation of pilot trials in clinical research in critical care. Crit Care Med. 2009; 37(Supplement):S69-S74.

144. Thabane L, Ma J, Cheng J, et al. A tutorial on pilot studies: the what, why and how. Medical Research Methodology. 2010; 10:1.

145. Kistin C, Silverstein M. Pilot Studies A Critical but Potentially Misused Component of Interventional Research. JAMA. 2015; 314(15):1561-1562.

146. Ameloot K, De Deyne C, Eertmans W, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. European Heart Journal. 2019; 369:2197–11.

147. Callaway CW, Donnino MW, Fink EL, et al. 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: Post–Cardiac Arrest Care. Circulation. 2015; 132:S465-S482.

148. Crepeau AZ, Rabinstein AA, Fugate JE, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest. Neurology. 2013; 80:339-344.

149. Foulon P, De Backer D. The hemodynamic effects of norepinephrine: far more than an increase in blood pressure! Ann Transl Med. 2018; 6(S1):S25-S25.

150. Sasson C, Rogers MAM, Dahl J, Kellermann AL. Predictors of Survival from Out-of-Hospital Cardiac Arrest. Circ Cardiovasc Qual Outcomes. 2010; 3(1):63-81.

151. Shoja MM, Tubbs RS, Shokouhi G, et al. The potential role of carbon dioxide in the neuroimmunoendocrine changes following cerebral ischemia. Life Sci. 2008; 83(11-12):381-387.

152. Buunk G, van der Hoeven JG, Meinders AE. Prognostic significance of the difference between mixed venous and jugular bulb oxygen saturation in comatose patients resuscitated from a cardiac arrest. Resuscitation. 1999; 41:257-262.

153. Lemiale V, Huet O, Vigué B, et al. Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. Resuscitation. 2008; 76(1):17-24.

154. Fink M. Cytopathic hypoxia in sepsis. Acta Anaesthesiol Scand. 1997; 110:87-95.

155. Taccone FS, Crippa IA, Creteur J, et al. Estimated cerebral perfusion pressure among post-cardiac arrest survivors. Intensive Care Med. 2018; 44(6):966-967.

156. Bouzat P, Suys T, Sala N, Oddo M. Effect of moderate hyperventilation and induced hypertension on cerebral tissue oxygenation after cardiac arrest and therapeutic hypothermia. Resuscitation. 2013; 84(11):1540-1545.

157. Connolly FD, Reitemeier J, Storm C, et al. Duplex sonography of cerebral blood flow after cardiac arrest — A prospective observational study. Resuscitation. 2014; 85(4):516-521.

158. Ameloot K, Genbrugge C, Meex I, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: Time to drop "one-size-fits-all" hemodynamic targets? Resuscitation. 2015; 90:121-126.

159. Brunauer A, Koköfer A, Bataar O, et al. The arterial blood pressure associated with terminal cardiovascular collapse in critically ill patients: a retrospective cohort study. Critical Care. 2014; 18(6):719.

160. Roth D, Van Tulder R, Heidinger B, et al. Admission blood pressure and 1-year mortality in acute myocardial infarction. Int J Clin Pract. 2015; 69(8):812-819.

161. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary. J Am Coll Cardiol. 2013; 61(4):1-26.

162. Thiele H, Ohman EM, de Waha-Thiele S, et al. Management of cardiogenic shock complicating myocardial infarction: an update 2019. European Heart Journal. 2019; 40(32):2671-2683.

163. Hochman JS, Sleeper LA, Webb JG, et al. Early Revascularization and Long-term Survival in Cardiogenic Shock Complicating Acute Myocardial Infarction. JAMA. 2006; 295(21):2511-2515.

164. Åneman A, Laurikkala J, Pham P, et al. Cerebrovascular autoregulation following cardiac arrest: Protocol for a post hoc analysis of the randomised COMACARE pilot trial. Acta Anaesthesiol Scand. 2019; 63(9):1272-1277.

165. Moseby-Knappe M, Mattsson N, Nielsen N, et al. Serum Neurofilament Light Chain for Prognosis of Outcome After Cardiac Arrest. JAMA Neurol. 2019; 76(1)64-71.