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A study of the inflammatory response and the circulatory failure after out-of-hospital cardiac arrest

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Circulation and Medical Imaging

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To my wife Elin, and my children Marcus André and Ann Madeleine.
To my parents Madli† and Knut, and my siblings Elisabet and Bjørn Endre.
To my in-laws Ann Jeannette and Bjørn.

Without whom none of this is possible, and with whom anything is possible.

- - -

"I write to find out what I think"

- Stephen King

Norsk sammendrag

EN STUDIE AV BETENNELSESREAKSJONEN OG SIRKULASJONSSVIKTEN ETTER HJERTESTANS UTENFOR SYKEHUS

Det har lenge vært kjent at hjertestans fører til en voldsom betennelsesreaksjon, som igjen fører til en dødelig flerorgansvikt. I 2019 ble 3715 personer forsøkt gjenopplivet i Norge, av disse ble 995 (27%) vellykket gjenopplivet og innlagt på sykehus. Etter 30 dager var 424 (11%) personer fortsatt i live.

Selv om mange av de innlagte pasientene etter hjertestans har antatt dårlig prognose, må man som intensivlege fokusere på de faktorer man nå kan gjøre noe med, i håp om å bedre utfallet. Flere forskere forsøker derfor å finne svaret på hvilke faktorer som kan gruppere hjertestanspasienter og hvilken målrettet terapi som de ulike gruppene har effekt av.

Fra januar 2016 til november 2017 inkluderte vi 50 pasienter som ble innlagt på St. Olavs Hospital etter hjertestans oppstått utenfor sykehus og fulgte dem tett, med hyppige målinger, i opptil seks dager etter innleggelse. Denne prospektive observasjonsstudien var godkjent av regional etisk komite, og alle pasienter, eller deres pårørende, samtykket til deltakelse.

Studien resulterte i tre publikasjoner som ligger til grunn for denne avhandlingen. Vi har undersøkt betennelsesreaksjonen og sirkulasjonssvikten som oppstår etter hjertestans utenfor sykehus. Vi har konsentrert oss om de første seks dagene av intensivforløpet.

Studie I tok for seg de store linjene i intensivforløpet etter hjertestans. Vi undersøkte både den overordnede utviklingen i sirkulasjonssystemet, organsvikt og forsøkte å finne pasientforløp som hadde fellestrekk. For å kunne vurdere fellestrekk mellom pasienter og utviklingen over tid, kodet vi målinger av sirkulasjonen (for eksempel blodtrykksnivå eller infusjonstakten av sirkulasjonsstøttende medikamenter) til sekvenser basert på et graderingssystem. Graderingssystemet var tredelt og gikk fra "stabil sirkulasjon" til "svært ustabil sirkulasjon". I tillegg kodet vi årsaken til at pasienten forlot studien ("overført til sengepost", "fortsatt intensiv pasient" og "død"). Til sammen gav dette oss en unik mulighet

til å vurdere alle de enkelte pasientforløpene i ett samlet bilde og dernest finne pasientforløp som hadde fellestrekk.
Vi fant at hjerteminuttvolumet steg, mens karmotstand falt i løpet av de første 48 timene etter hjertestans, og at majoriteten av pasientene stabiliserte seg innen 72 timer. Vi identifiserte fire undergrupper av pasientforløp med liknende utvikling og alvorlighetsgrad av sirkulasjonssvikt. Sjokkbar hjerterytme var assosiert med et fordelaktig forløp, mens høyt syreoverskudd i blodet ved innleggelse, som gjenspeiler langvarig tid uten tilstrekkelig sirkulasjon, var assosiert med et dårligere forløp.

I **studie II** så vi først på sammenhengen mellom hjertestans og betennelsesmarkører i blodet, og dernest på sammenhengen mellom betennelsesmarkører og henholdsvis sirkulasjonssvikt og død. Vi fant at lang tid til gjenvunnet egensirkulasjon og høyt melkesyrenivå i blodet ved innleggelse var assosiert med komplement-aktivering, betennelsesfremmende cytokiner og markører for skade på åreveggen. Disse betennelsesmarkørene var igjen assosiert med lavere hjerteminuttvolum, blodtrykk, karmotstand og behov for sirkulatorisk støttende behandling i den initiale fasen av intensivforløpet. Dessuten var høye nivåer av komplementet TCC og cytokinet IL-6 ved innleggelse assosiert med 30-dagers dødelighet.

I **studie III** undersøkte vi detaljer i sirkulasjonssvikten mer inngående. Vi ønsket å beskrive nærmere hvordan de to mekanismene, tap av karmotstand og hjertesvikt, bidro til sirkulasjonssvikten. Ved å beregne oksygen- og energileveransen, samt å vurdere dette i lys av markører på vevsmetabolisme, dannet vi oss et mer komplett bilde av hva svikten består i. Samtidig analyserte vi om høye nivåer av ulike betennelsesmarkører og hjertemarkører i blodet påvirket behandlingslengde med sirkulasjonsstøttende medikamenter og væskeinfusjoner.
Vi fant at oksygen- og energileveransen tok seg opp, og vevsmetabolismen bedret seg i løpet av 48 timer. Til tross for at den matematisk beregnete karmotstanden var fallende, var det dominerende kliniske bildet en sirkulasjon i bedring. Høye nivåer av hjertesviktmarkøren pro-BNP, og ikke betennelsesmarkører, de første 52 timene, var avgjørende for hvor lenge pasienten hadde behov for det sirkulatorisk støttende medikamentet noradrenalin.

Kandidat

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Table of contents

Preface

My residency in anesthesiology started at Levanger hospital under Gunnar Engstrøm's and Robert Pedersen's proficient guidance in 2010. After two years of commuting to Levanger from Trondheim, I changed to a residency at St. Olav's University Hospital. There I met Stein Dragsund and later Idar Kirkeby-Garstad. Gunnar, Robert, Idar and Stein were knowledgeable, always curious and willingly instructed young colleagues everything from theoretical circulatory physiology to practical Swan-Ganz use. I am grateful for the influence they had on my early clinical career.

During my rotation in cardio-thoracic anesthesiology, I met Nils-Kristian Skjærvold and Petter Aadahl. They convinced me that clinical medicine in combination with research could provide an exciting and varied career. Influenced by them I enrolled in 2013 in the PhD-program with the project "Blood flow distribution in hemorrhage and sepsis, the link between macro- and micro-hemodynamic". Together with Oddveig Lyng, we created an animal model to study circulatory shock. Unfortunately, refurbishment of the animal laboratory in combination with a new financing model put an early end to the project. Still, we were able to publish one article.[1] I am grateful for everything I learned about animal handling, laboratory work and translational research.

However, I now had to look around for an alternative research project. In 2015 I got in touch with Pål Klepstad. Together with Daniel Bergum, Knut Bjørnstad, Thomas Skaug and Magnus Løberg, we designed a new project: "Characterization of the post-cardiac arrest syndrome", where we combined advanced hemodynamic measurements with meticulous blood sampling at all hours throughout the day. Inflammatory biomarkers work in mysterious ways, and the clinical interpretation is often difficult as they have multiple, context-specific and synergistic effects, where much is still unknown. Fortunately, I got invaluable help from Tom Eirik Mollnes, Thor Ueland and Jan Kristian Damås in analyzing and interpretation. The article on inflammation (paper II) was commented on in the editorial![2] With one-minute resolution of electronic sampled clinical variables during up to six days of critical care, the amount of data towered up quickly. Luckily, Ørjan Gundersen and Trond Nordseth provided excellent computable help to organize and analyze this behemoth of data.

The project was going to be more ambitious than I ever had imagined, and to top it all off, I also became locally responsible for the "Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM2)" – trial. Thankfully, I got devoted support from Helle Merethe Næss and Therese Marie Erbe to handle the complex follow-up procedures. However, the TTM2-trial did not end up as part of my doctoral thesis.[3]

Even though I sometimes wondered what I had embarked on, I now look back with gratitude and pride over everything I learned on this winding path to a doctorate.

Although this thesis lists only one author, this project has in reality been teamwork by many knowledgeable and generous colleagues and friends. There are many people I would like to acknowledge, but the following persons have been particularly invaluable in completing my PhD-project. Firstly, I would like to thank all the nurses at the cardiovascular and the main intensive care unit. Your positive can-do attitude around-the-clock made all the difference! Secondly, I would like to thank my supervisors Nils-Kristian, Petter, Trond and Pål for insightful and patient guidance and excellent feedback. Thirdly, I would like to thank my collegial friends Magnus and Daniel, for their extraordinary contributions, tremendous working capacity and never-ending enthusiasm. Fourthly, Samarbeidsorganet HMN-NTNU, that granted me a scholarship and patiently extended the time frame. Fifthly, to my superiors, Sigurd Fasting, Øystein Karlsen, and Guri Greiff, who often gave me time for research during busy working days. Finally, my deepest gratitude is to my family; to my parents Madli† and Knut, to my siblings Elisabet and Bjørn Endre, to my in-laws Ann Jeannette and Bjørn. With unhesitating faith and support they encouraged me to pursue my goals. To my lovely wife Elin, in particular, who amidst all of the demands of family life, always were steadfastly supportive and loving through my mood swings and my absence from home. To my treasured children Ann Madeleine and Marcus André, who always remind me of what is the most important, and thus help me rearrange my priorities.

Halvor Langeland
Trondheim, January 2022

"Without data you're just another person with an opinion."

- W. Edwards Deming

List of papers

This thesis is based on three studies that resulted in the following papers:

PAPER I

Circulatory trajectories after out-of-hospital cardiac arrest: a prospective cohort study

Langeland H, Bergum D, Nordseth T, Løberg M, Skaug TR, Bjørnstad K, Gundersen Ø, Skjærvold NK and Klepstad P.

BMC Anesthesiology. 2021;21(1):219

PAPER II

The inflammatory response is related to circulatory failure after out-of-hospital cardiac arrest: a prospective cohort study

Langeland H, Damås JK, Mollnes TE, Ludviksen JK, Ueland T, Michelsen AE, Løberg M, Bergum D, Nordseth T, Skjærvold NK and Klepstad P.

Resuscitation. 2021;170:115-125

PAPER III

The characteristics of circulatory failure after out-of-hospital cardiac arrest: a prospective cohort study

Langeland H, Bergum D, Løberg M, Bjørnstad K, Skaug TR, Nordseth T, Klepstad P and Skjærvold NK.

Open Heart. 2022;9(1):e001890

Abbreviations

AHA	American Heart Association
ANOVA	Analysis of variance
AUC	Area under the curve
Pro-BNP	Pro-brain natriuretic peptide
CCI	Charlson comorbidity index
CI	Confidence interval
CO	Cardiac output
CPC	Cerebral performance category
CPO	Cardiac power output
CPR	Cardio-pulmonary resuscitation
CRP	C-reactive protein
CVP	Central venous pressure
C3bc	Complement 3b (activated)
DO_2	Oxygen delivery
Ea	Aortic elastance
ECMO	Extracorporeal membranous oxygenation
ER	Emergency room
Hgb	Hemoglobin
HR	Hazard ratio
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
IL	Interleukin
ILCOR	International liaison committee on resuscitation
IQR	Interquartile range
mCPIS	Modified clinical pneumonia infection score
MAP	Mean arterial pressure
MPAP	Mean pulmonary arterial pressure
OHCA	Out-of-hospital cardiac arrest
OR	Odds ratio
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PCAS	Post-cardiac arrest syndrome

PaO_2	Arterial partial pressure of oxygen
PvO_2	Venous partial pressure of oxygen
$P(v\text{-}a)CO_2$	Venous-to-arterial carbon dioxide difference
RCT	Randomized controlled trial
ROSC	Return of spontaneous circulation
SAPS	Simplified acute physiology score
SD	Standard deviation
SDF	Sidestream dark-field
SOFA	Sequential organ failure assessment
SpO_2	Peripheral transcutaneous oxygen saturation
SvO_2	Mixed venous oxygen saturation
SV	Stroke volume
SVR	Systemic vascular resistance
SW	Stroke work
TCC	Terminal complement complex
VAD	Ventricular assist device
VO_2	Oxygen consumption

Introduction

CARDIAC ARREST

Sudden out-of-hospital cardiac arrest (OHCA) is the third leading cause of death in Europe, with an estimated yearly incidence of 56 (range 27–91) per 100 000 persons.[4]

In 2019, 3715 persons received cardio-pulmonary resuscitation (CPR) after OHCA in Norway.[5] This approximates an incidence of 70 per 100 000 persons. Of these patients, 85% received bystander CPR by laypeople for a median of nine minutes before ambulance personnel arrived. Of the 995 persons admitted to hospital, 424 patients survived more than 30 days. Ninety-three percent of the survivors had a good neurological outcome at hospital discharge.[5] 2019 represent a slight increase in reported incidence from previous years.[6] Compared with the rest of Europe, Norway has an exceptional high rate of bystander CPR, which is reflected in one of the best survival rates on the continent.[4]

The etiology of cardiac arrest can be broadly categorized into cardiac (e.g. ischemic heart disease, arrhythmias and cardiomyopathies) and non-cardiac (e.g. hemorrhage, asphyxia and infections) causes.[7] Cardiac arrest is also usually classified into whether it occurred inside or outside a hospital, because patient morbidity, surveillance, and proximity to advanced cardiovascular life support are different. Although, cardiac etiology is the main cause of cardiac arrest in both groups, there are differences in etiological subgroups, incidence and survival rate.[8]

Over the last five decades, the chance of successful resuscitation, i.e. return of spontaneous circulation (ROSC), has improved through information campaigns and training of both laypeople and professional response teams in, respectively, basic and advanced cardiovascular support.[7,9,10] Although, there has been some improvements in the survival after in-hospital cardiac arrest, the survival after cardiac arrest in general is still low.[8,10] Survival to hospital discharge is approximately 10–12% for out-of-hospital cardiac arrest and 18–25% for in-hospital cardiac arrest.[4,8] Even though rapid recognition and treatment of cardiac arrest are the most important factors for a better outcome, much research is also focused on how to reduce the already inflicted injury through improved care in the intensive care unit (ICU).[11]

POST-CARDIAC ARREST CARE

In 1972, Vladimir Negovsky urged his colleges to address the importance of treating the "post-resuscitation disease", which he believed to be a neglected part in the treatment of patients with cardiac arrest.[12] The "post-resuscitation disease", is now referred to as the "post-cardiac arrest syndrome" (PCAS) and compromise a) brain injury, b) myocardial dysfunction and c) systemic inflammation after whole body ischemia and reperfusion injury.[13] In addition, the pathological process that caused the cardiac arrest, and the patient's comorbidity, complicates the development of the PCAS.

With the exception of 24 hours of therapeutic hypothermia, and early percutaneous revascularization of the culprit lesion in case of myocardial ischemia, there is no specific treatment of PCAS beyond standard critical care support.[14–16] Thus supportive measures have so far been based on general critical care recommendations built on experience from similar conditions.[13,14,17] However, organ failure after cardiac arrest might have unique characteristics that need special attention. This is exemplified by the need to sufficiently perfuse the post-ischemic brain without unnecessary strain on the post-ischemic heart.

The current general recommendations focus mainly on respiratory support, circulatory support, and neuroprotective strategies. More precisely, this means to achieve normoxia and normocapnia within the limits of protective ventilation, to avoid hypotension and achieve adequate urine output with decreasing lactate levels, and avoidance of hypoglycemia, hyperglycemia, seizures and fever.[14]

The most common cause of in-hospital death after cardiac arrest is irreversible brain damage.[18,19] Brain tissue has high metabolism, but low oxygen reserves.[20] This makes brain tissue especially vulnerable to anoxia and hypoxia, which occurs during reduced or absent circulation, before and during the resuscitation attempt.[21,22] After 72 hours unresponsiveness, patients should be examined for signs of irreversible brain damage. Based on the result of this multimodal evaluation of neurological prognosis, further treatment should be planned or withdrawn.[14] In a specific effort to reduce the brain injury and improve the outcome, patients receive therapeutic hypothermia during the first 24 hours of intensive care treatment.[14,22]

Target temperature management

It has long been known that different cells types have different metabolic activity, and thus oxygen requirements, and that this metabolism and oxygen consumption, is temperature dependent.[23] Encouraged by earlier animal research on cardiac arrest and hypothermia, two small human trials were published in 2002 that investigated the effect of mild hypothermia after cardiac arrest.[24,25] Both trials showed a survival benefit, with improved neurologic outcome, for patients cooled to 32–34 ºC for 12–24 hours. However, the trials suffered from methodological biases, where the development of fever in the control group was especially criticized.[26] Fever in the early vulnerable phase after anoxic brain injury is known to worsen the outcome.[27] In 2013 and 2021, two large randomized double-blinded trials (RCT) published no difference in patient outcome for target temperature of 33 ºC versus 36 ºC, and 33 ºC versus <37.8 ºC, respectively.[3,28] Consequently, the effect of mild hypothermia, beyond the embedded avoidance of fever, is in question. This conclusion will likely impact current treatment and future guidelines.

THE INFLAMMATORY RESPONSE

Inflammation is the immune system's response to harmful stimuli. Both tissue damage and presence of foreign material (e.g. bacteria and viruses) provoke a reaction that coalesce to a common signal pathway, which in turn elicit a broad and complex inflammatory response to combat and repair the injury or infection (Figure 1). Dependent on the extent of the injury or infection the local inflammatory response can, through feedback loops, escalate and become systemic.

The development of a systemic inflammatory response, that involves the whole body and can elicit remote organ injury, is therefore dependent on the balance between pro- and anti-inflammatory chemical mediators, such as cytokines.[29]

In cardiac arrest, ROSC after successful resuscitation provokes a massive inflammatory response due to whole-body ischemia and reperfusion injury (i.e. tissue injury),[30] which resembles the immunologic and coagulation pattern observed in severe sepsis (Figure 1).[31]

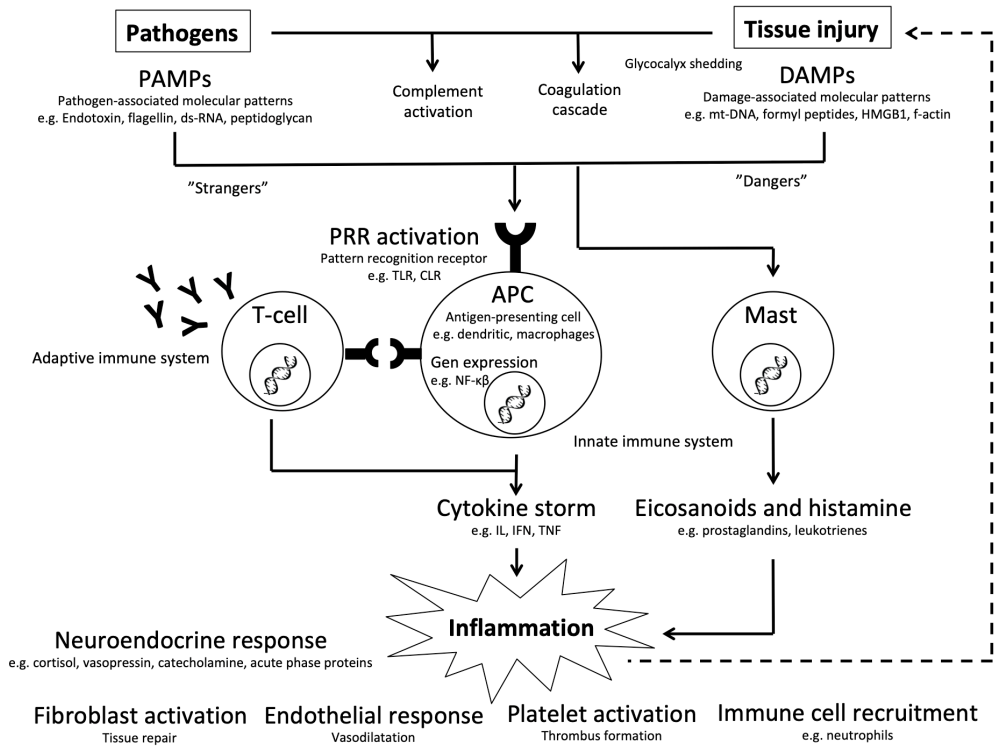

Figure 1. A simplified presentation of the inflammatory response

The inflammatory response is broad and complex, involving many chemical mediators, cascades and feedback loops that are not yet fully understood. The balance between pro- and anti-inflammatory cytokines modulates the scale of the response.
Illustration by H. Langeland.

Several studies have explored cytokine patterns as biomarkers for morbidity and mortality in sepsis.[29,32–34] In comparison, few human studies have evaluated the inflammatory and endothelial response in PCAS. So far, elevated interleukin (IL) 6 and complement factor 3 have been found to be associated with mortality, whereas elevated trombomodulin, IL-6 and IL-10 have been associated with multiple organ failure.[35–44] Furthermore, even fewer studies specifically investigated the relationship between inflammatory response and hemodynamic variables, and only IL-6 has been associated with increased vasopressor support.[45]

ORGAN FAILURE AFTER CARDIAC ARREST

The ischemia and reperfusion injury, and the subsequent inflammatory response, is associated with multiple organ failure after cardiac arrest. However, not all organ systems are affected equally. Cerebral, respiratory and circulatory failure is common in PCAS, whereas coagulation, liver and renal function is usually only mildly affected.[19] Even if renal and liver

failure is less common, more sensitive measurements of kidney and liver damage after cardiac arrest demonstrate an association with increased mortality.[18,19,46,47] Furthermore, failure of other organ systems than the brain, also have major long-term consequences. A large Finnish retrospective cohort study showed that degree of initial organ failure, excluding brain damage, was associated with increased mortality and increased healthcare-associated costs the following year.[48]

The circulatory failure

In 2002 Laurent *et al.* reported on how the hemodynamic characteristics developed after cardiac arrest in normothermic patients.[49] In his study, hemodynamic instability occurred after a median of 6.8 hours after OHCA and was characterized by low cardiac index and low filling pressures. After 24 hours the cardiac index improved, but a superimposed vasodilatation occurred that led to delayed discontinuation of vasopressors and need for volume expansion. Recovery was usually within three days, and hemodynamic status did not predict neurologic outcome.[49]

A similar circulatory pattern, i.e. increase in cardiac output and decrease in systemic vascular resistance (SVR) during the first 24 hours, was also shown in hypothermic (33 °C) patients.[50–52] Recently, in two studies based on data from the target temperature trial, Bro-Jeppesen *et al.* compared macrocirculatory variables in patients cooled either 33 or 36 °C.[53,54] Patients cooled to 33 °C had a significantly lower cardiac index and heart rate, higher SVR index and lactate levels and increased need for vasopressor support, than patients cooled to 36 °C. However, patients already in circulatory shock at admission were excluded.[53,54] Circulatory shock was defined as either a systolic blood pressure ≤90 mmHg, or the need of fluids and/or vasopressors to keep systolic blood pressure >90 mmHg. This is a widely used simplified definition of the circulatory component in the "Brussels score" where circulatory shock (systolic blood pressure ≤90 mmHg) were classified from mild to extreme based on fluid responsiveness and degree of acidosis.[55] Later, a post-hoc analysis of the target temperature trial showed that mild hypothermia did not lead to survival benefit for patients in circulatory shock on admission.[56]

With exception of Laurent *et al.*, who used continuous infusion of adrenaline, none of the recently mentioned studies reported detailed information about the vasoactive medications used to achieve the hemodynamic results.

The visual echocardiographic pattern of the post-resuscitation myocardial dysfunction is described as ranging from global dysfunction to regional abnormalities and a more Takotsubo-like pattern.[57] In a study of repeated echocardiographic measurements after OHCA, Jentzer *et al.* demonstrated a mean increase in ejection fraction of 11% from the initial to the follow-up measurement.[52] A smaller improvement between measurements was associated with mortality.

A prominent feature in inflammatory circulatory shock is the discrepancy between the macro- and microcirculatory indices, where microcirculatory failure can be demonstrated before evidence of macrocirculatory failure, and sustains after macrocirculatory restoration.[58–60] Three small studies on microcirculatory alterations after cardiac arrest showed that the microvascular flow impairment was similar to the one seen in sepsis, and independent of macrocirculatory variables.[61–63] Still, patients admitted to ICU after cardiac arrest, are usually treated without the aid of advanced invasive cardiovascular monitoring. Thus, the current guideline on circulatory treatment in PCAS largely emphasis avoiding hypotension, i.e. keep mean arterial blood pressure (MAP) above 65 mmHg, as this target has been shown to decrease mortality.[64,65]

KNOWLEDGE GAPS IN CIRCULATORY FAILURE AFTER CARDIAC ARREST

In 2008, the International Liaison Committee on Resuscitation (ILCOR) stated that there are several knowledge gaps concerning the PCAS.[13] More specific, questions regarding the pathophysiologic mechanisms, time course, and treatment of myocardial dysfunction and impaired oxygen delivery and utilization were raised.[13] In 2015, the American Heart Association's (AHA) recommend that researchers also considered patients' heterogeneity, and preferably tailored treatment to the specific subgroups.[17] Later statements and guidelines have not specifically addressed the knowledge gaps regarding the underlying pathophysiology, but rather focused on the insufficient evidence of specific hemodynamic treatment goals in PCAS.[14,66–68]

A failure to explain is often caused by a failure to describe and I believe there are still knowledge gaps regarding the understanding of inflammatory response and the subsequent circulatory failure in PCAS. Thus, studies that address the above raised questions are still warranted.

Aims

In this thesis I want to contribute to the knowledge regarding the PCAS in the belief that better understanding may lead to better future treatment of this condition. The PCAS is a complex condition, involving many organ systems. I will, therefore, concentrate on the inflammatory response and circulatory development during the first week of intensive care treatment. Thus, the primary aim of this study is to give a detailed description of the overall circulatory trajectory after cardiac arrest, with emphasis on identifying the elements in and prediction of circulatory failure, and its relationship with inflammatory biomarkers.

To achieve the aims we identified the following research questions:

- What are the characteristics of circulatory failure in PCAS?
- Is the circulatory failure homogenous, or heterogeneous with subgroups of patients with similar circulatory trajectories?
- What is the inflammatory response measured by inflammatory and endothelial biomarkers in PCAS?
- What is the association between inflammatory response and circulatory failure after cardiac arrest?
- What is the relative contribution between myocardial dysfunction and systemic inflammation in circulatory failure after cardiac arrest?

Materials and methods

This section is common to the three studies presented, unless otherwise stated.

DESIGN

The study is a prospective, single-center, observational cohort study of patients admitted to hospital with ROSC after OHCA. Patients were included between January 2016 and November 2017.

SETTING

St. Olav's University Hospital is a 938-bed tertiary hospital in Trondheim, Norway, serving a population of approximately 700,000.[69] The study took place at the main intensive care unit and the cardiovascular intensive care unit (both units referred to as ICU in the text).

ELIGIBILITY

All adult patients, both comatose and awake, admitted to the ICU with obtained ROSC after OHCA was assessed for eligibility and included in the study if the eligibility criteria were met.

Exclusion criteria

Exclusion criteria were age <18 years, pregnancy, transferal from another hospitals, assumed septic or anaphylactic etiology of cardiac arrest, decision to limit life-sustaining therapy upon arrival, acute cardiothoracic surgery, intervention with extracorporeal membranous oxygenation (ECMO) or a ventricular assist device (VAD) before arrival in the ICU.

STUDY PERIOD AND CENSORING

Patients followed the study protocol from time of admission and the following five days, or until the patient died, until ECMO or VAD was initiated, acute cardio-thoracic surgery, decisions to limit life-prolonging therapies was taken, or transfer to a general ward or another hospital. Day zero had variable length depending on the time of inclusion, whereas day one started the following morning at 06:00.

SAMPLE SIZE

This is a descriptive study and no formal sample size calculation was performed.[70] However, based on sample size from similar observational studies, we decided to include 50 participants.

ROUTINE POST-CARDIAC ARREST CARE

The physician in charge decided on the general treatment of the patients. The decision was based on the hospital's treatment guidelines, and the overall treatment recommendation were not changed based on participation in the study.

The routine treatment after OHCA at St Olav's University Hospital is briefly outlined below.

Cardiac interventions

In patients where ischemic etiology for the cardiac arrest was suspected, coronary angiography and revascularization by percutaneous coronary intervention was performed.

The cardiologist decided which other heart-specific therapies, such as intra-aortic balloon pump (IABP) and anticoagulation, the patient should receive.

Target temperature management

All comatose patients received Target Temperature Management (36 °C) for 24 hours, and were then gradually rewarmed (0.5 °C/hour) to 37 °C. Hypothermia was induced either invasively (Icy Zoll Circulation Inc., USA) or externally (CureWrap 3500, MTRE, Israel).

Sedation and analgesia

Sedation and analgesia were initiated with the combination of propofol and remifentanil. However, if the patient were perceived as too circulatory unstable or longer duration of ventilation was anticipated, the medications were changed to midazolam and fentanyl. Sedation was titrated to Motor Activity Assessment Scale 0−1 during hypothermia, and later titrated to the lowest dose necessary for adequate patient comfort. A muscle relaxant, cisatracurium, was not routinely used but initiated if indicated (e.g. shivering or ventilation failure).

Cardiovascular support

The primary circulatory treatment goals followed the hospital's treatment guidelines and were:

- MAP ≥65 mmHg.
- Urine output ≥0.5 ml/kg/hours.
- No clinical signs of tissue hypo-perfusion, such as cold, clammy skin and extremities, prolonged capillary refill time, diminished urine output, increasing lactate and decreasing base excess, decreasing central/mixed venous oxygenation and if not sedated; deteriorating mental status.

Physicians in the ICU were instructed to optimize the circulation after the following algorithm: In the presence of hypotension (<65 mmHg) and tissue hypo-perfusion, first assess volume status (i.e. preload) by echocardiographic assessment and/or presence of pulsus paradoxus (i.e. pulse pressure variation >10%). If the patient was assumed to be a fluid-responder, repeated fluid boli of 250 ml was given until the circulatory goals were achieved. If the patient was assumed not to respond or tolerate additional fluids, or if a combined medical approach was indicated, noradrenaline and/or dobutamine were given depending on whether vasoconstrictive and/or inotropic effects were indicated. If the vasoplegia was not improved by a relative high dose of noradrenaline (≥0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), an addition of a fixed dose of vasopressin (0.4 $mU \cdot kg^{-1} \cdot min^{-1}$) was considered. This sequence of action was based on the assumed least myocardial oxygen consumption and is in accordance with a recently published recommendation on circulatory optimization.[71]

Respiratory support

A SERVOi ventilator (Maquet Siemens, Germany) administered ventilation. Ventilator modus were either pressure controlled or pressure support. The ventilator settings were adjusted to achieve a tidal volume of 6–8 ml/kg, a positive end-expiratory pressure of 8 cmH_2O (adjusted to improve oxygenation), a respiratory rate that gave a arterial partial pressure of carbon dioxide within the normal range, and a fraction of inspired oxygen that gave an oxygen saturation above 95%.

Nutrition

Enteral nutrition was given as soon as possible, and gradually increased until 25–30 kcal/kg/day was achieved. If enteral nutrition was not feasible, total parenteral nutrition was introduced at day four. If metabolic control of blood sugar levels was necessary, a continuous infusion of rapid acting insulin was given and adjusted to stabilize the blood sugar between 5–10 mmol/l.

Infection control

Antibiotics were not given routinely, but administered if there was a clinical suspicion of an infection.

Neuroprognostication

In patients, who remained unresponsive after sedation had been stopped, an assessment of hypoxic brain injury was usually initiated after day three. The assessment was based upon the results from clinical examination, serum neuron-specific enolase concentrations, computer tomography scanning, and neurophysiological examination (e.g. somatic evoked potential and electroenchepalogram).

STUDY PROCEDURE

All comatose patients without contraindications received a pulmonary artery catheter (PAC) (Swan-Ganz CCombo, Edwards Lifesciences, USA) for continuous central hemodynamic measurements. Twice daily, we calibrated the PAC oxygen saturation sensors and measured wedge pressure.

The electronic critical care management system (Picis CareSuite, Optum Inc., USA) recorded heart rate, arterial blood pressure, central venous pressure (CVP), peripheral transcutaneous oxygen saturation (SpO_2), temperature, fluid balance, medications and respiratory support. In patients with a PAC, the system collected cardiac output, pulmonary artery pressure, mixed venous saturation, and calculated systemic vascular resistance. From the pre-hospital report and hospital record, we registered data according to the Utstein guidelines,[72] Charlson comorbidity index (CCI, Appendix 1),[73] and information on assessment and treatment.

We calculated Simplified Acute Physiology Score 2 (SAPS-2, Appendix 2) 24 hours after admission, whereas modified Clinical Pneumonia Infection Score (mCPIS, Appendix 3) and Sequential Organ Failure Assessment (SOFA, Appendix 4) scores were calculated daily.[74–76] After 30 and 180 days, we obtained survival status and Cerebral Performance Category (CPC, appendix 5) from the hospital record.[77]

Thrombocyte and white blood cell count, creatinine, urea, c-reactive protein (CRP), haptoglobin, troponin T, pro-brain natriuretic peptide (pro-BNP) and bilirubin serum concentrations were measured at inclusion and every day at 06:00 a.m. during the study period. Every six hours, we obtained an arterial blood gas sample.

BLOOD SAMPLE HANDLING

Blood samples for inflammatory biomarkers were taken at inclusion and thereafter every morning the patient remained in the ICU until day five. After gentle mixing, the blood samples were placed vertical for 30 minutes in ambient temperature, and then centrifuged at 2200 *g* for 10 minutes. The supernatant was frozen to -80 °C within 1 hour from sampling.

Plasma levels of the following inflammatory cytokines were analyzed with Bio-Plex Pro Human Cytokine 27-plex Assay (Bio-Rad Laboratories, USA); tumor necrosis factor, interferon gamma, interleukin 1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10, interferon-inducible protein 10, eotaxin, macrophage inflammatory protein 1 beta, regulated on activation normal T-cell expressed and secreted, basic fibroblast growth factor and platelet derived growth factor-BB. The two complements, terminal complement complex (TCC) and activated complement 3b (C3bc), were measured by enzyme-linked immunosorbent assay, according to the International Complement Standard #2.[78]

Plasma levels of endothelial and platelet biomarkers; intercellular adhesion molecule 1, vascular cell adhesion molecule 1, syndecan-1, vascular endothelial (VE) cadherin, p-selectin and von Willebrand's factor, were measured by enzyme immunoassays in duplicate using commercially available antibodies (R&D Systems and Agilent, USA) in a 384 format using a combination of a CyBi-SELMA pipetting robot (Analytik Jena, Germany) and an automatic washer-dispenser (BioTek, USA). Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (BioTek, USA).

Measurements under lower limit of detection were set to 0.01 in the statistical analysis.

HEMODYNAMIC CALCULATIONS

Flow measurement

Cardiac output (CO) is the product of stroke volume (mL per beat) and heart rate (beats per minute) and measured in L/min. Although the normal resting CO is ~4–8 L/min, SvO_2 is considered to be a better indicator to evaluate the situational adequacy of the CO.[79]

Energy delivery

The total energy delivery from the heart to the circulation is in the form of a pressurized volume, and can be measured either per beat as stroke work (SW) or per minute as cardiac power output (CPO). CPO is measured in Watt (W) and calculated by CO (L/min) · MAP (mmHg) divided by 451. The normal resting CPO is ~1 W where <0.54 W is indicative of hemodynamic compromise.[80,81] SW is measured in Joule (J) and calculated by CPO · 60 divided by heart rate.

Estimates of vascular resistance

Afterload is defined as the wall tension in the ventricle during the ejection phase. Clinically, afterload is estimated as the resistance to the ejection, and SVR is the most used vascular resistance estimate. SVR is calculated by (MAP (mmHg) − CVP (mmHg)) · 79.9 divided by CO (L/min), with a normal range ~800–1200 dynes·sec/cm^5. However, a more "physiologic" per beat estimation of vascular resistance is aortic elastance (Ea), which can be approximated non-invasively by systolic blood pressure (mmHg) · 0.9 divided by stroke volume (mL). The normal range is 1.4–3 mmHg/mL.[82,83]

Oxygen delivery, consumption and extraction

Oxygen delivery (DO_2) were calculated by 0.134 · Hgb (g/dL) · SpO_2 (%)· CO (L/min) and oxygen consumption (VO_2) by 0.134 · Hgb (g/dL) · (SpO_2 − SvO_2 (%)) · CO (L/min).[23] The arterial and venous partial pressure of oxygen (PaO_2 and PvO_2) have a negligible contribution to the total oxygen delivery and consumption, and thus omitted from the above calculations. The oxygen extraction ratio (O_2ER) can be calculated by DO_2 divided by VO_2, or

approximated by 1 − SvO_2.[79] Thus the balance between DO_2 and VO_2 is reflected in the SvO_2.

ETHICAL CONSIDERATION

Assessment of safety

Besides establishing and calibrating a PAC and drawing blood for biomarker analysis at a maximum of six time-points the study did not involve other interventions than routine care after OHCA. The insertion of PAC is associated with both potential benefits and risks. A PAC provides the clinicians with an opportunity for better guidance of circulatory support, including a more precise administration of fluids and vasoactive medications. Placement of PAC leads to serious complications in approximately 1 in 1000 patients.[84] Although the use of PAC has been debated, a large meta-analysis from the Cochrane Collaboration concluded, with high evidence, that PAC neither increased mortality nor lengthened the stay in ICU or hospital.[85] Furthermore, a large study from the Attend registry showed a survival benefit in patients with decompensated heart failure when diagnosis and treatment were guided by a PAC.[86]

We therefore anticipated that the patients included would experience neither benefit nor harm from participation in the study. The study would bring forward general knowledge that may benefit future patients suffering from the same medical condition.

Ethical approval and consent

It was important that the study was initiated in the acute phase following OHCA. Therefore, comatose patients were not able to provide informed consent at time of inclusion. The Regional Committee for Medical and Health Research Ethics approved the study, including that the patient could be included if the physician in charge of the patient care had no objections and a consent from next-of-kin was obtained at the earliest feasible moment (REK Midt, No. 2015/1807). Afterwards, we obtained a deferred consent from all patients who regained their capacity to give an informed consent.

STATISTICAL ANALYSIS

Data from the electronic patient record were organized with the software Matlab (Mathworks Inc., USA). All statistical analyses, except those concerning sequence and cluster analysis, were performed with Stata version 16.1 (StataCorp LCC, USA). R version 3.6.0 with the package "TraMineR" was used for the sequence and cluster analysis in study I.[87,88] The Forest plots that visualize the odds and hazard ratios in this thesis were created with GraphPad Prism version 9.2.0 (GraphPad Software, USA).

Study I

An event (e.g. motor vehicle accident) occurs at a certain point in time, and has no duration. However an event, or a combination of events, might provoke a change in state (e.g. from healthy to injured patient). In contrast, a state has duration, and lasts until a new event (e.g. operation) induce a change into a new state (e.g. from injured to stabilized patient). Multiple events can occur at the same time, but states are mutually exclusive.[89] Moreover, a state transition *per se* can also be considered as an event. The longitudinal sequence of events, state transitions and states forms a "trajectory" (e.g. a hospital stay).

Similar trajectories can be grouped into clusters based on one or more common attributes. These common attributes can be based on similar starting point (e.g. a demographic characteristic), similar outcome (e.g. death) or similar sequence pattern (i.e. similar trajectories). Similar trajectories can be defined in several ways, such as number or pattern of recurrent sub-sequences, resemblance to one or more identified typical trajectories, or a similarity score (i.e. "distance") between trajectories.

All elements within or between sequences can be analyzed. For instance, the probability for transitions between states (i.e. events) can be estimated in a multi-state competing risk model. In a multi-state model, the observed person or object can transit between several predefined states that "compete" with each other (Figure 2A). The transition probabilities, as well as the time-to-events of interest can be properly analyzed applying methods in survival analysis. Furthermore, the trajectory properties, e.g. frequently recurring or especially turbulent patterns can be identified with sequence analysis, and similarities between trajectories can be found and hierarchically grouped using cluster analysis (Figure 2B).

Survival analysis and some cluster analysis allow for right censoring, where patients with limited follow-up time, which equals sequences of different length, can be included in the analyses.

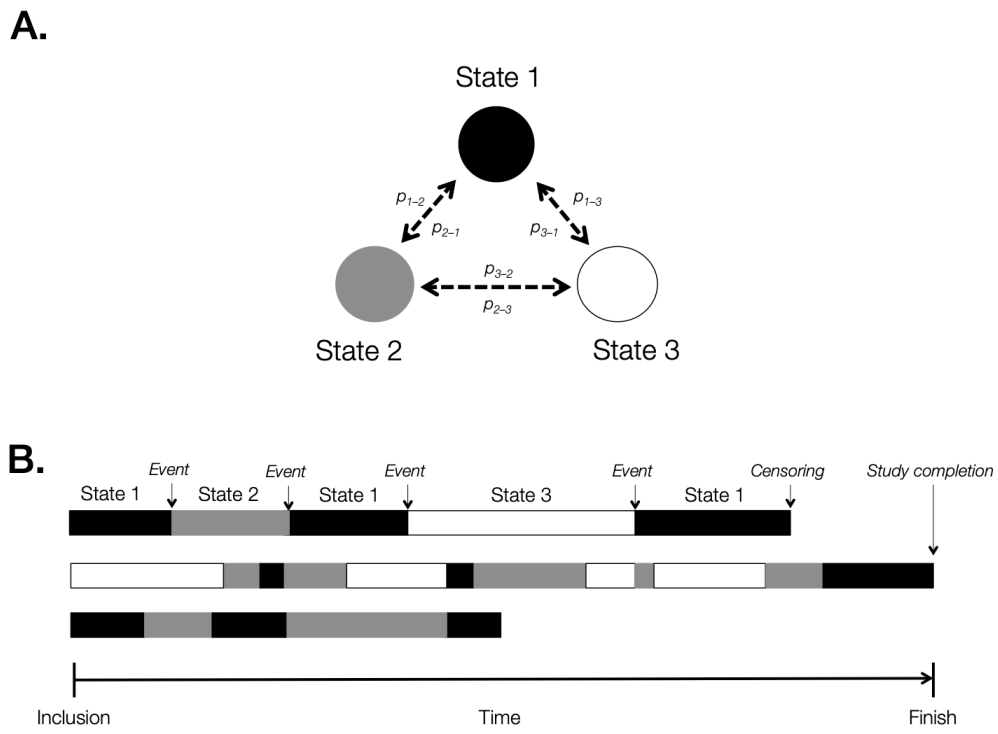

Figure 2. State transitions and trajectories

Panel A shows an example of possible transitions between different states and their different probabilities (i.e. a "Markov chain"). **Panel B** shows examples of trajectories (i.e. longitudinal sequence of states) during the study period. An event induces a transition from one state to another. Different trajectory length indicates different follow-up time due to censoring before study completion. Illustration by H. Langeland.

In study I, the patients' circulatory measurements were classified every hour into one of three circulatory states; 'undisturbed', 'disturbed' or 'severely disturbed', based upon the least favorable measurement. We used predefined values of mean blood pressure, heart rate, lactate concentrations, fluid resuscitation, vasoactive medications and the need for mechanical circulatory support (Table 1).[90] There is no consensus on the definition and classification of circulatory instability. For this reason, hemodynamic variables and corresponding cut-off

values, were based upon general guidelines, clinical relevance and availability during routine monitoring of critically ill patients.

Central venous oxygen saturation was initially included in the classification, but was not used due to few measurements.[90] The reason for the low number of measurements during the intensive care was that all the lumens of the central venous catheter were usually occupied by drug or fluid administration and to obtain a sample implied an interruption of those infusions. Unfortunately, we had not anticipated this problem when designing of the study.

Table 1. Circulatory states*

Variables	Undisturbed	Disturbed	Severely Disturbed
Mean arterial pressure, mmHg	≥65	45–64	<45
Heart rate	51–100	<50, 101–130	≤40, >130
Lactate, mmol/l	<2	2–4	>4
Fluid resuscitation, l/hours	<0.5	0.5–1.9	≥2
Noradrenaline, $\mu g \cdot kg^{-1} \cdot min^{-1}$	<0.1	0.1–0.29	≥0.3
Dobutamine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	No	<10	≥10
Vasopressin	No	No	Yes
Adrenaline	No	No	Yes
Levosimedan	No	No	Yes
Aorta balloon pump	No	No	Yes

* Every hour a patient was classified into undisturbed, disturbed or severely disturbed circulation according to the least favorable measurement at that time (e.g. isolated mean arterial pressure of 40 mmHg is sufficient to classify a patient to have severely disturbed circulation).

We assessed the patients' transitions between the circulatory states of: 'undisturbed', 'disturbed' or 'severely disturbed' in a multi-state model.[91] For instance, a patient may transit back and forth between 'undisturbed', 'disturbed' and 'severely disturbed' state and these transitions recorded as a sequence of states (i.e. a trajectory).[92]

In addition, we considered the reason for censoring to be informative, and therefore we coded it into one of three "absorbing states" in the sequence and cluster analysis (Figure 3). The three absorbing states were 'transferred to ward in circulatory stable condition', 'still treated in ICU' and 'death'.

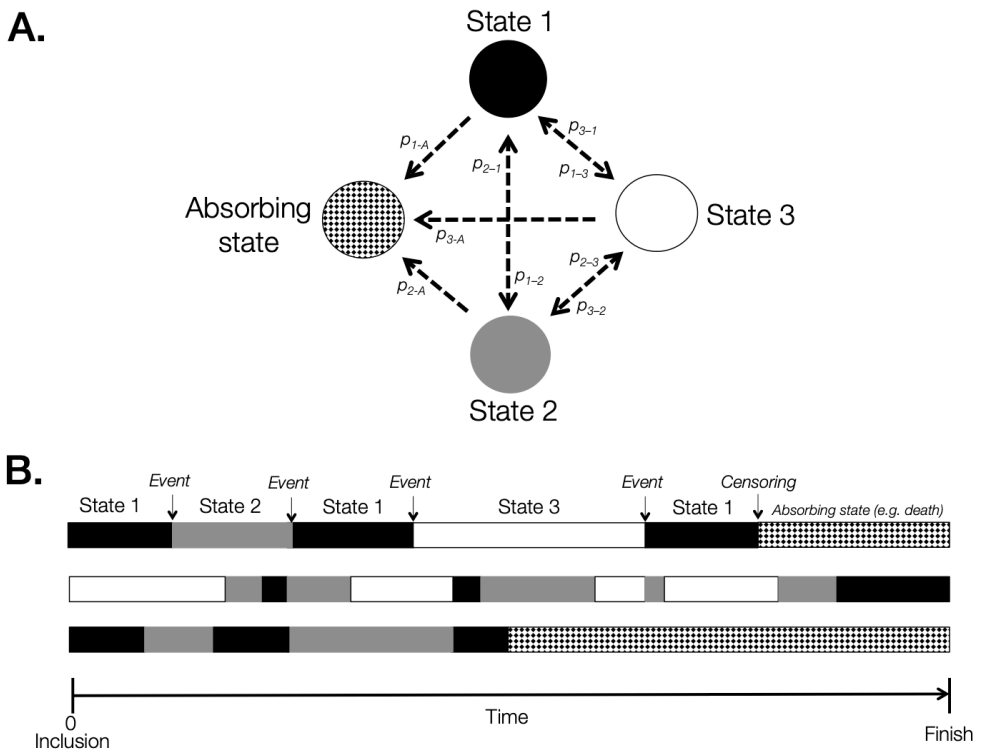

Figure 3. State transitions and trajectories with coded absorbing state

A state without a return possibility is called an "absorbing state". **Panel A and B** shows the analysis in Figure 2 with censoring coded as an absorbing state. Illustration by H. Langeland.

As sequence and cluster analysis, we used pairwise optimal matching and Ward's minimal variance method to group the sequences hierarchically into clusters of similar trajectories.[88] In optimal matching, dissimilarity between trajectories is measured by how many changes needed to be made (the penalty cost) for editing a sequence into another, and the result of all pairwise matches are recorded in a matrix (Figure 4A). As recommended, the penalty cost of insertion or deletion was set to 1 and the cost of substitution was based on the transition rate.[88]

Ward's method is a computationally intensive algorithm that evaluates all possible trajectory combinations to build a cluster hierarchy (Figure 4B). The hierarchy is organized bottom-up, based on the least within and between cluster variances, until the preset number of clusters is identified.[88] Based on previous studies on intensive care populations, we aimed at identifying four clusters.[93,94]

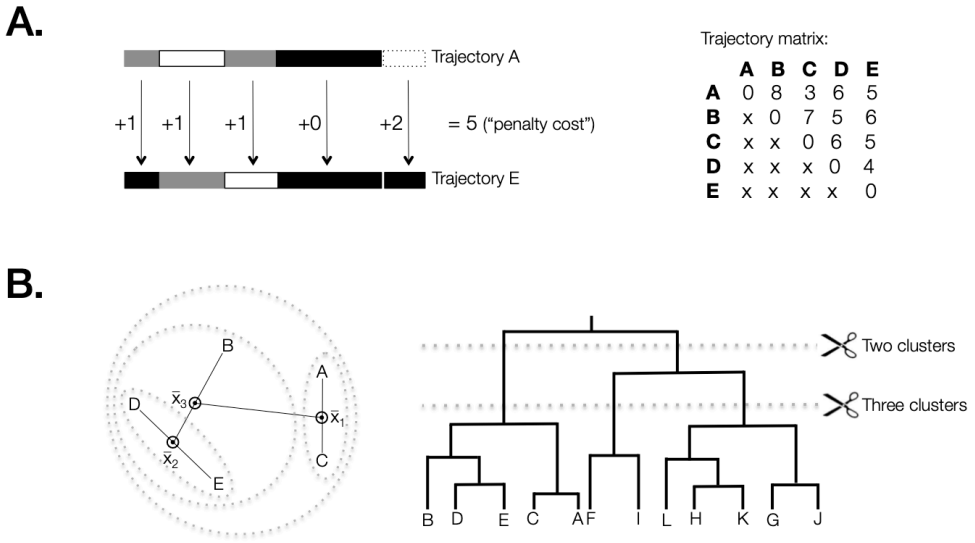

Figure 4. Sequence and cluster analysis

Panel A shows examples of sequence editing and the associated cost. Different edits have different cost. The total "penalty cost" is a measurement of dissimilarity between trajectories. A matrix is created to keep track of the dissimilarity between all the trajectories. **Panel B** shows an example of how clusters are formed based on least within-cluster variability from the cluster mean (i.e. variance). The result can be organized into a "dendrogram", which is grown bottom-up and cut at the level of preset number of identified clusters. Illustration by H. Langeland.

We used ordered logistic regression to estimate the odds ratio (OR) for cluster membership based on independent factors related to patient demographics, the resuscitation episode and status at hospital admission. In ordered logistic regression the OR between clusters are equal, and the odds ratio is interpreted as the odds of a higher (here: worse) cluster membership. Based on predictors from previous studies, we included age, comorbidity, shockable initial rhythm, time to ROSC, base deficit at admission and circulatory shock at admission to predict cluster membership, and the anticipated circulatory trajectory.[53,95]

Study II

To describe the circulatory effects and the risk of mortality mediated by the inflammatory response after cardiac arrest, we divided the analysis into three steps. First, we assessed the associations between Utstein cardiac arrest variables and biomarkers applying linear regression models. Second, we assessed the association between biomarker concentrations and circulatory variables (noradrenaline dose, fluid infusion, CO, SVR, and MAP) at admission

and day two using linear regression models. For circulatory variables we calculated the mean value over the period starting 30 minutes before and ending 30 minutes after each blood sample collection. In both analyses, the associations were assessed at day zero (i.e. admission) and on day two (after ~35–40 hours) in order to capture both the immediate and a delayed inflammatory response and circulatory effects after cardiac arrest. Finally, we used logistic regression of biomarkers at admission to estimate the OR for 30-day mortality.

All biomarkers were binary logarithmic (log_2) transformed to obtain normal distributions. Only biomarkers consistently associated with circulatory variables (more than two measurements with p value <0.1) in the daily univariable analysis were included in the backward elimination of variables in the multivariable regression models. We used the coefficient of determination (R^2) to assess the models' explanatory capabilities. In the case of heteroscedasticity, a regression model with robust standard error was used, and strongly collinear predictors (variance inflation factor >10) were omitted from the analysis.

To describe the biomarker alteration over time, we stratified the study population into three groups, based on whether they were dead, still in ICU, or transferred to ward in stable condition, by day five. First, we showed stratified graphs of biomarker concentrations over all days. Then, we used one-way analysis of variance (ANOVA) and Tukey's method to determine if biomarker concentrations between groups were significantly different at day zero and day two.[96]

Study III

The mean circulatory development over time was graphically presented, and the differences between mean level of CPO, SW, Ea, SV, MAP and noradrenaline dosage at four and 48 hours after ICU admission were tested by Welch's unequal variance *t*-test.

Contrary to the two previous studies, the graphs origin were set to time of emergency call and smoothed with a three-hours moving average to better visualize trends.

We used survival analysis to explore the time to discontinuation of noradrenaline and daily negative fluid balance as a marker of circulatory stabilization. As the main etiologies of circulatory shock in PCAS are inflammatory and/or cardiogenic, we compared high versus

low levels of IL-6, syndecan-1, CRP, pro-BNP and troponin T. Based on available blood samples, we stratified the population by the median of the area under the curve (AUC) for the biomarker measurements the first 52 hours after the emergency call. Furthermore, we used Cox regression to estimate the hazard ratio (HR) with 95% confidence intervals (CI).

In univariable logistic regression, we tested the association between biomarkers, that where identified in the Cox regression as significantly affecting the duration of circulatory support, and demographic variables.

Results

DEMOGRAPHICS

During the study period 71 patients were admitted with ROSC after OHCA. Of these patients, 65 were assessed for eligibility, and 50 were included in study I and II. Fifteen patients were excluded for the following reasons: seven because life-sustaining treatment was withdrawn upon arrival at the hospital, two had septic causes of cardiac arrest, two were not in need of intensive care treatment, two patients received VAD, one received ECMO and one patient underwent immediate cardiothoracic surgery. In study III additionally eight patients, who were awake at admission, were excluded, and only the 42 comatose patients were analyzed. A comparison of the study populations is presented in Table 2.

Table 2. Demographic comparison of study populations

Patient characteristics	Study I and II N = 50	Study III N = 42
Demographic		
Age, years, mean (SD)	62.7 (15.3)	64.8 (14.5)
Male sex, no. (%)	40 (80)	35 (83)
Body mass index, mean (SD)	27.5 (6.6)	27.7 (7)
Charlson comorbidity index, median (IQR)	3 (2)	3 (3)
Cardiac arrest		
Bystander witnessed, no. (%)	42 (84)	34 (80)
Bystander performed CPR, no. (%)	44 (88)	37 (88)
First monitored rhythm, no. (%)		
Shockable	39 (78)	31 (73)
Non-shockable	11 (22)	11 (27)
Median time to ambulance arrival, min (IQR)	9.5 (8.5)	10.5 (10)
Median time to ROSC, min (IQR)	24 (18)	26 (16)
Presumed etiology, no. (%)		
Cardiac	42 (84)	34 (81)
Non-cardiac	8 (16)	8 (19)
Admission		
Comatose,[a] no. (%)	42 (84)	42 (100)
Circulatory shock,[b] no. (%)	18 (36)	18 (42)
Arterial blood gas, mean (SD)		
pH	7.18 (0.14)	7.17 (0.15)
Base excess, mmol/l	-9.4 (7.4)	-9.7 (7.7)
Lactate, mmol/l	6.7 (4.2)	6.9 (4.5)
Percutaneous coronary intervention, no. (%)	21 (42)	17 (40)
Pulmonary artery catheter, no. (%)	30 (60)	30 (71)
SAPS II,[c] mean (SD)	62 (19)	68 (12)

Study population III compromised the comatose patients from study I and II.

[a] Comatose were patients that were intubated and gave no contact (GCS <8).

[b] Systolic blood pressure <90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.

[c] Score after 24 hours.

CPR: cardio-pulmonary resuscitation; GCS: Glasgow coma scale; IQR: interquartile range; ROSC: return of spontaneous circulation; SAPS: Simplified Acute Physiology Score; SD: SD: Standard deviation.

Patients in study population III have more often non-cardiac etiology, non-shockable first monitored rhythm and longer time to ROSC than patients in study population I and II.
PAC was inserted in 30 of the included comatose patients. The primary contraindications were bleeding diastasis after percutaneous coronary intervention, implantable cardioverter-defibrillator or technical difficulties.

MORBIDITY AND MORTALITY

During the first four days, the patients had median SOFA scores between 10 and 11 points, which improved on the fifth day to a median of 7.5 points. The most frequent organ system failures were circulatory, neurologic and respiratory. The median mCPIS score peaked on day four, when 12 of 27 patients had a score ≥6 and 26 of 27 patients received antibiotics.

Sixteen patients died within 180 days (Table 3). Six patients died within 48 hours, predominantly from refractory circulatory shock or multi-organ failure (4 of 6 patients), while ten patients died later, mostly due to irreversible brain injury (8 of 10 patients). All eight patients who were awake at admission survived with good neurologic outcomes (defined as CPC 1). Twenty-six of the patients who were comatose at admission were discharged alive from the hospital. Twenty-two of these had a good neurologic outcome (CPC 1) after 180 days.

Table 3. Morbidity and mortality

Outcome	All N = 50	Comatose[a] N = 42 (84%)	Awake N = 8 (16%)
Length of stay			
Days in ICU, median (IQR)	6.5 (9)	8 (8)	2.5 (1.5)
Hours on respirator, median (IQR)	65 (150)	94 (145)	0 (0)
Days in hospital, median (IQR)	14 (13)	15 (13)	13 (10)
Cerebral performance category 180 days			
I – normal, no. (%)	30 (60)	22 (52)	8 (100)
II – moderate disability, no. (%)	2 (4)	2 (5)	0 (0)
III – severe disability, no. (%)	2 (4)	2 (5)	0 (0)
IV – coma or vegetative state, no. (%)	0 (0)	0 (0)	0 (0)
V – dead, no. (%)	16 (32)	16 (38)	0 (0)
Mortality			
30–days, no. (%)	15 (30)	15 (36)	0 (0)
180–days, no. (%)	16 (32)	16 (38)	0 (0)

[a] Comatose were patients that were intubated and gave no contact (GCS <8) at admission.
GCS: Glasgow coma scale; ICU: intensive care unit; IQR: interquartile range.

STUDY I – MAIN RESULTS

In study I, we analyzed 869 circulatory state transitions in 49 patient trajectories. One patient was excluded due to technical difficulties with data sampling. Approximately half of the patients were in severely disturbed circulatory state at admission. However, most patients stabilized in a better circulatory state after 72 hours. At the end of the study period 14 (28%) of the patients had been transferred to ward in a stable clinical condition, 23 (46%) were still treated in the ICU, and 12 (24%) had died.

We identified four sub-groups (i.e. clusters) of patients with similar circulatory trajectories. Patients in Cluster 1, which compromised 28% of the study population, were in general stabile within 48 hours and transferred to ward in clinical stable condition. In Cluster 2 (46% of the study population), patients were mostly in a disturbed circulatory state and remained under intensive care treatment during the study period. Patients in Cluster 3 (8% of the patients) and Cluster 4 (16% of the patients) were in disturbed and severely disturbed circulatory state until death within 96 and 24 hours, respectively.

In the multivariable ordered logistic regression analysis, base deficit at admission was significantly associated with a higher cluster membership and thus a worse circulatory trajectory (OR 1.18 per mmol/L, 95% CI 1.03–1.35), whereas an initial shockeable cardiac rhythm was associated with a lower cluster membership and therefore a more favorable circulatory trajectory (OR 0.07, 95% CI 0.01–0.46) (Figure 5).

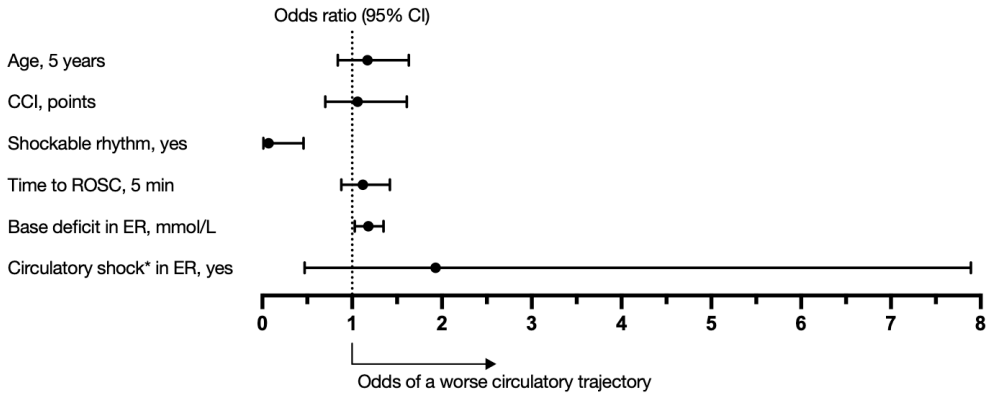

Figure 5. The association between demographic variables and cluster membership

In ordered logistic regression, the odds ratio among clusters are equal, and the odds ratio should be interpreted as the odds of a higher cluster than the compared cluster when the explanatory variable is increasing by one unit and all other variables are held constant. CCI: Charslon comorbidity index; CI: confidence interval; ER: emergency room; ROSC: return of spontaneous circulation. *Systolic blood pressure <90 mmHg or in need of vasopressors.

STUDY II – MAIN RESULTS

In study II, blood samples were drawn at inclusion and every morning during the ICU stay. The development of inflammatory biomarkers during the study period, showed in general a decreasing trend and a dose-response relationship; where patients who died by day five, had higher concentrations than patients who remained in ICU by day five and both patient groups had higher levels than patient transferred to ward in stable clinical condition within day five.

In the multivariable linear regression model, long time to ROSC and high lactate concentrations at admission were significantly associated with higher levels of TCC, C3bc, IL-1ra, IL-6, IL-8 and syndecan-1, but lower levels of VE-cadherin, at admission. Higher levels of C3bc, IL-6, IL-8 and syndecan-1, and lower level of VE-cadherin, was associated with lower MAP, CO and SVR, and higher noradrenaline dosages, higher SOFA scores, and increased fluid support at admission and day two.

The OR for mortality within 30 days was 1.86 (95% CI 1.02–3.40) and 2.01 (95% CI 1.20–3.37) for each two-fold increase in plasma concentration of TCC and IL-6 at admission, respectively (Figure 6).

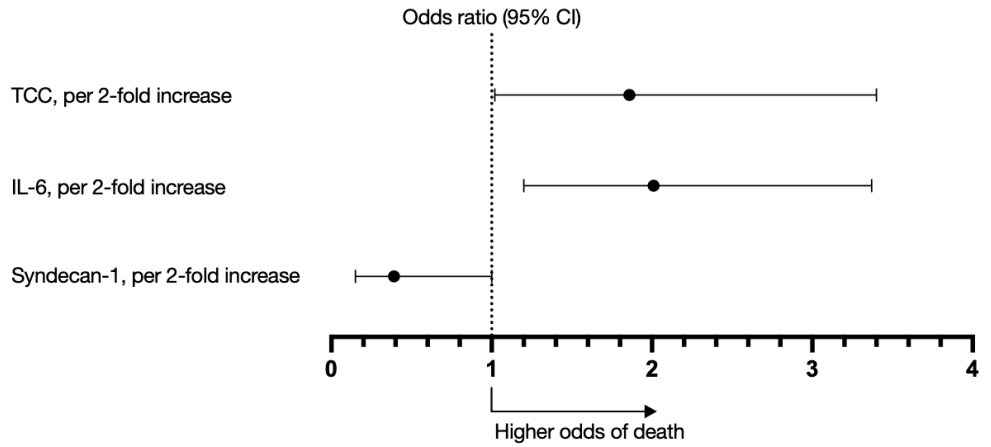

Figure 6. The association between 2-fold increase in biomarker and 30-days mortality

CI: confidence interval; IL-6: interleukin-6; TCC: terminal complement complex.

STUDY III – MAIN RESULTS

In study III, macro- and microcirculatory development were analyzed, together with comparison of time to discontinuation of circulatory support between high and low levels of inflammatory and cardiac biomarkers.

In general SV, SW, CPO and DO_2 increased during the first 48 hours. Simultaneously, Ea fell. Noradrenaline doses were gradually reduced, and after 48 hours, the mean dose of noradrenaline was halved, while the MAP had been maintained above 65 mmHg. Mean fluid balance was negative by day four. Both VO_2 and SvO_2 were stable during the study period. Lactate and venous-to-arterial carbon dioxide difference ($P(v\text{-}a)CO_2$) levels were normalized within 24 hours.

There was a significant difference in time to noradrenaline discontinuation between low versus high pro-BNP groups (HR 0.45, 95% CI 0.21–0.96), but not between the other groups (Figure 7). Furthermore, we found no significant difference between groups regarding time to negative fluid balance.

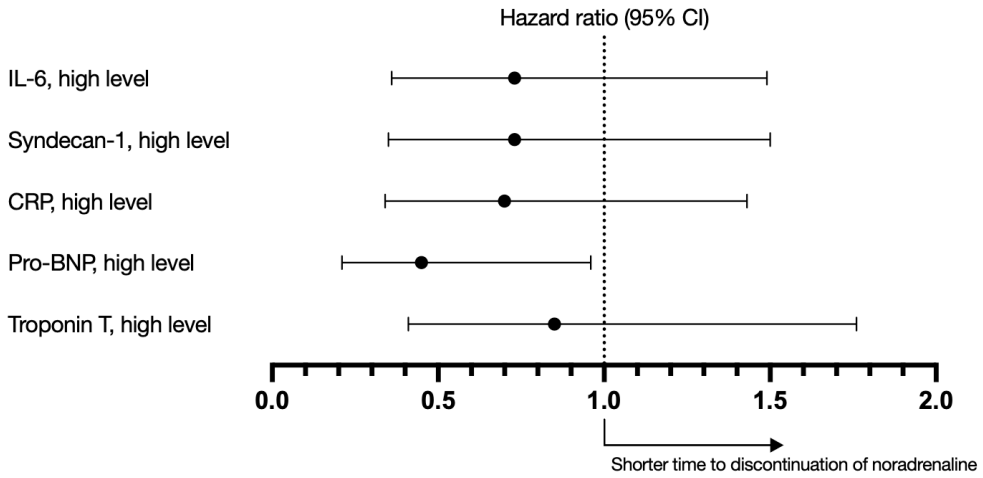

Figure 7. The hazard ratio for discontinuation of noradrenaline between high and low biomarker level.

A median split of the biomarkers AUC during the first 52 hours dichotomized the patients.

AUC: area under the curve; CI: confidence interval; CRP: C-reactive protein; IL-6: interleukin-6; Pro-BNP: Pro brain natriuretic peptid.

We found no significant association between patients in the high pro-BNP group and demographic variables.

Discussion

METHODOLOGICAL CONSIDERATIONS AND VALIDITY

In this clinical study, we have collected raw data outside the controlled environment of a laboratory. Field work like this imposes particular logistic challenges.[97] As the results and the conclusions are no more trustworthy than the data collected, getting all the details right is the key to high-quality clinical research.

Many studies fail due to too complicated and overambitious protocols that are not grounded in normal hospital routines. To overcome the most obvious biases (i.e. systematic errors), field investigators need to combine both traditional research skills, such as accurate measurements with minimal variance, with social skills, such as patient recruitment and collaboration with hospital staff from different departments. Clinical experience is an advantage to achieve around-the-clock adherence to the research protocol and collection of data, without compromised patient care or unnecessary strain on personnel.

Study design

We used a prospective observational design in the three studies that compromise this thesis. Although, a randomized controlled trial is the superior study design in theory, it requires a clearly defined intervention and an observational study can be more suitable for answering the research question.[97] Firstly, an observational study can bring forth general knowledge of the current situation and generate hypothesis that later can be tested in a randomized controlled trial. Secondly, an observational design is less demanding both financially and on personnel resources. Thirdly, it can be unethical to randomize a patient to either a hazardous therapy or no therapy at all. Therefore, in lack of direct evidence, circumstantial evidence from an observational study might be acceptable.

Data collection and systematic error

The clinical study team involved four clinician investigators who were on-call around-the-clock for screening and inclusion, initiating and overseeing data sampling, and drawing, preparing and storing blood samples. With the exception of two months (July and August) in 2016, and three months (June, July and August) in 2017, admitted OHCA patients were consecutively included in the study within few hours of their cardiac arrest. Engaging fewer

study investigators increases transparency and compliance with the study protocol, which in turn reduces sampling variability and missing values.

All surveillance data were collected using the automatic electronic documentation system installed at the ICU. With this electronic documentation system sampling interval can be adjusted to the wanted level of resolution. Standard sampling interval at our ICU is set to 15 minutes, which were reduced to every minute in study participants. By comparison, standard sampling interval in hand-written ICU charts is usually every 15–60 minutes. Thus, an electronic system gives access to precise information with higher time resolution.

Where to set time zero (i.e. origin) for measurement depends on what you want to study. In study I we were interested in the clinical trajectory during the ICU stay and set origin to time of ICU admission, whereas in study III we were interested in the underlying circulatory pathogenesis and set origin to time of the emergency call.

Laboratory analysis of biomarkers

Blood samples were drawn for all patients immediately after ICU admission and thereafter every morning in the ICU. The preparation and storing were done according to a strict protocol by one of the four trained clinician investigators. The blood samples were stored at -80 °C for up to 22 months, until being shipped to the laboratories in Bodø and Oslo for analyses. During transportation by World Courier (AmerisourceBergen), the samples were preserved in cooled containers.

The inflammatory biomarkers were analyzed at the Research Laboratory at Nordland hospital and endothelial biomarkers at the Research Institute for Internal Medicine at Oslo University Hospital. The reported intra- and inter-assay coefficients of variation were <10% for all enzyme immunoassays, which is considered good. Measurements below lower detection limit were set to 0.01.

Although the strict protocol and professional handling of the blood samples is strength of our study, three aspects need to be addressed. First, many biomarkers show diurnal variation.[98] Except for the first blood sample, which was drawn shortly after arrival at the ICU, the following samples were drawn every morning. This makes makes the values from day one and

onwards comparable. Second, even at -80 °C biomarkers degrade over time thus making concentration measurements less robust, and storage for longer periods than two to three years is not recommended.[98] We were able to analyze all our samples within two years, and long storage time should not influence our result. Third, multiple freeze-thaw cycles can affect the biomarker concentration, and should therefore be kept to a minimum, preferably under three cycles.[98] Our samples underwent two shipments and two freeze-thaw cycles, which could possibly affect our results.

Statistical analysis and random error

Multiple testing

In all three papers included in this thesis, we have performed analysis on several endpoints using the generally accepted type I error rate of 5%. A type I error is to make the incorrect conclusion that the observed effect in the sample is also present in the population (i.e. rejecting a true null hypothesis).[99,100] A 5% error rate implies that one test in 20 will be a false positive, but with multiple testing, the risk of a type I error increases.

Therefore, we discussed using a more stringent criterion of statistical significance, such as the popular Bonferroni correction, to avoid this risk. However, the use of adjusted significance levels is debatable for several reasons.[101] Firstly, grouping all null hypotheses into on universal null hypothesis is usually "irrelevant" to most inferences. Secondly, in an effort to decrease the risk of type I errors, adjusting the significance level increases the risk of type II errors, which are equally false (e.g. many biological variables are not independent of each other, rendering an adjustment too conservative). Finally, it is not clear which tests that should be adjusted for (e.g. all tests performed or all tests presented in this and future papers?).[101] We landed on describing the hypothesis, and its pre-planned tests, and presented the unadjusted numbers for all to appraise.

For the same recommended reasons we tried to keep significance testing to a minimum, and instead provided estimates with 95% confidence intervals.[102,103] Compared with *p*-values, confidence intervals provide additional information (i.e. effect size together with an estimate of precision or uncertainty) that contributes to the scientific inference of clinical relevance.[102]

Sample size

In this descriptive and exploratory study, the circulatory trajectory, abnormal biomarkers and outcomes were largely unknown and we did not perform a formal sample size calculation.[70] Instead, we based the sample size on the norm from similar studies describing pathophysiology.[42,50,104] With a limited number of patients in this study, there is a good chance that we have committed a type II error in some of the analyses. A type II error is to make the incorrect conclusion that the observed effect in the sample is not present in the population (i.e. failure to reject a false null hypothesis).[99] The type II error rate is usually set to 10%, implying that one in ten tests will be a false negative.[99] This type II error rate gives a statistical power, i.e. the probability of correctly rejecting the null hypothesis, of 90%.[99]

Statistical tests used in the papers

Most statistical models rely on a normal (or at least a symmetrical) distribution, independent data, equal variance between groups, censoring unrelated to outcome, and a linear relationship. Biased assumptions, such as a skewed distribution, can be corrected by transforming the data (e.g. logarithmic transformation), or using a "robust" model that is less sensitive to long-tailed distributions, i.e. outlier-resistant.[99] With a relative low sample size in our study, we expected a higher variability of the sample mean (i.e. standard error), and therefore checked all regression models for unequal variance (i.e. heteroscedasticity) and applied a robust model if unequal variance was suspected. For the same reason, we replaced the more common Student's *t*-test with Welch's *t*-test. To achieve normal distribution for the regression and ANOVA analysis all biomarkers were logarithmically transformed.

In paper I, we used sequence and cluster analysis to group similar sequences into clusters. This is a complex procedure that relies heavily on computer algorithms.[88] The penalty cost of sequence editing is debatable, and a different value could have resulted in a different pairwise matching and perhaps cluster membership. However, the four clusters described in this study seem clinically reasonable. As these clusters can be hierarchically arranged, ordered logistic regression was suitable. The coding of clinical variables into sequences relied on categories that were based on cut-off values from general accepted guidelines, but a different cut-off value for the variables could a resulted in a different categorization, and thus different sequences. Still, the high numbers of transitions (869 events), and that clinical relevant variables (blood pressure, heart rate and dose of noradrenaline) most frequently induced the change in category give our model credibility.

In paper II, the biomarker levels were compared with the corresponding circulatory variable (i.e. mean value of the time interval around the biomarker measurement) in the regression analyses. By contrast, in paper III, we used survival analysis and stratified the population by median split of the AUC of the IL-6, syndecan-1, CRP, pro-BNP, and troponin T concentrations the first 52 hours after the emergency call. Categorization of continuous data gains simplicity and makes clinical application easier, but it also comes with a cost.[105] Firstly, setting a cut-off value of a continuous variable is always a choice, and thus debatable. For a variable where a higher value means more severe disease, a higher cut-off value means that the specificity increases (fewer healthy people will be categorized as sick), while the sensitivity decreases (more sick people will be categorized as healthy). If a lower cut-off value is chosen, then the opposite will occur. Since all biomarkers were elevated above their "normal" range, we chose the median to create a "low" versus "high" group. However, the median will be different between studies, which makes comparisons more challenging and also the application to diverse clinical settings. In addition, a different time interval for the AUC could have yielded a different result. Still, IL-6, syndecan-1, troponin T and pro-BNP concentrations peak early and decline rapidly after OHCA, thus the majority of the area under the curve was covered during the first 48 hours. Secondly, categorization of continuous data contribute to loss of statistical power and precision of the estimates, which makes erroneous statistical inference more likely.[105] Nonetheless, dichotomizing the sample population based on AUC, rather than a single blood sample, is considered a more robust approach when a physiologic relationship, and not an early prediction (e.g. at admission), is the aim for the study.[106]

The variables that were considered for inclusion in the regression analyses were chosen based on clinical experience and literature search. Still, we needed to restrict the list of potential candidate variables, which we did in a step-wise process. First, we chose variables that were consistently associated with the outcome, i.e. that were more than two associations with $p < 0.1$ in the univariable regression model. This process reduced the list of candidate variables in the multivariable model from 22 to 10. Secondly, we removed strongly correlated (i.e. collinear) variables, since they violated the independent data assumption. Thereafter, we used backward elimination of the variables with the highest *p*-value until only those with $p < 0.1$ remained. Although backward elimination is an acceptable method, it is generally more correct to let the experts on inflammation do the final selection of candidate variables.[107]

In an effort to achieve an "unbiased" estimate of the association between exposure and outcome, a Directed Acyclic Graph is a valuable tool to visualize which elements to control for in the analysis (Figure 8).[108] Briefly, these diagrams link elements by arrows that represent direct causal effects of one element on another.

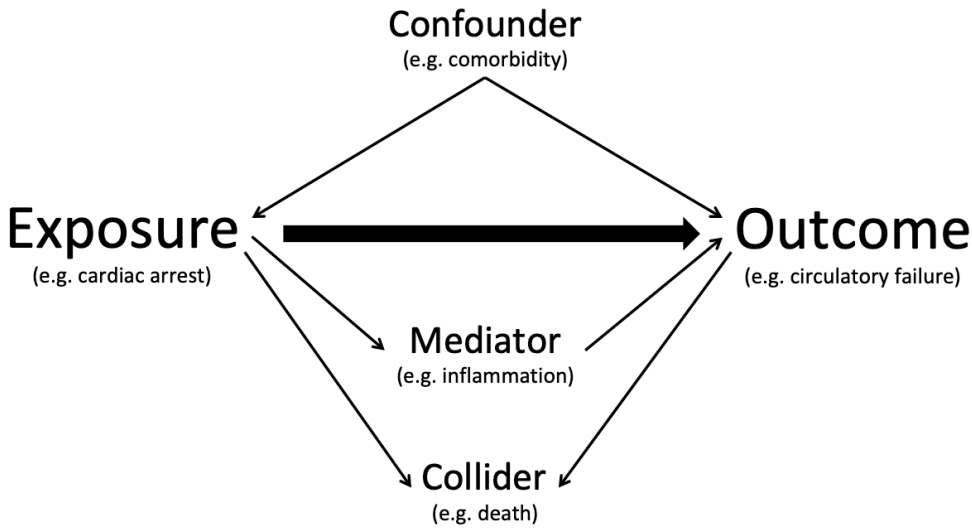

Figure 8. Example of a Directed Acyclic Graph.

In analyzing the association between exposure and outcome, both confounder biases and mediators should be included as covariates in the analysis. Collider biases should not be included, as they will lead to spurious associations.[109] Illustration by H. Langeland.

Although, highly collinear variables were removed before the analysis, we witnessed increasing significance in the multivariable model for some predictors, which indicate the presence of a "suppressor variable". A suppressor variable correlates with other independent variables and suppresses some of the variability in the correlated variable, increasing its effect size and improving the overall predictability of the model. Even when the suppressor variable is uncorrelated with the outcome, it is considered that the risk of excluding a relevant variable outweighs the risk of including an irrelevant variable.[110]

The multivariable models had in general a high coefficient of determination (R^2), indicating a good explanatory capability. However, it could also indicate "over-fitting". An over-fitted model might be better at predicting in the specific study sample, but unfortunately less generalizable to other populations.[111]

In paper III, we used Cox regression analysis to estimate the ratio of the hazards for an event (i.e. noradrenaline discontinuation and negative fluid balance) between the "high level" and "low level" (reference) groups. An explicit assumption for the results from a Cox regression to be applicable at all time-points throughout the observed period, is that the hazards are proportional, which means that the ratio between the hazards is always the same. In medical research, HR are rarely constant over time, and thus the assumption is frequently violated.[112] By examination of the Kaplan-Meier curves in paper III we see that the probability of an event in the groups decreases non-proportionally over time. However, this does not mean that the results from the Cox regression cannot be used, but rather that presented HR should be interpreted as a weighted average for entire the observation period.[112] An HR below one indicates that an event is overall more likely in the reference group, whereas a ratio above one indicates that event is less likely in the reference group.

External validity

To which extent the results from the study provide a correct basis for understanding and treating similar patients elsewhere is referred to as external validity.[97] The single-center design with limited number of patients increased the chance that the study cohort might not reflect the population in other health care systems. On the other side, the study had broad inclusion criteria and few exclusion criteria; the patients were consecutively assessed for eligibility, and treated in accordance with current international guidelines. Therefore, to our experience the study cohort reflects a typical ICU population after OHCA and the study results seemed clinically reasonable, and therefore assumed to be generalizable.

INTERPRETATION OF RESULTS

The overall circulatory development in PCAS

In paper I we described the two-phased circulatory development, where the initial phase was characterized by low CO and high SVR, that later subsided to high CO and low SVR.

Laurent *et al.* have previously described this phenomenon, and interpreted it as a resolving myocardial stunning, followed by peripheral vasodilatation due to systemic inflammation.[49] We saw that after liberal fluid resuscitation and noradrenaline infusions during the first 12

hours, the need for circulatory support was gradually reduced in the following days. The majority of patients had stabilized within 72 hours, as seen either by having reached an 'undisturbed' circulatory state or that they had achieved negative daily fluid balance. In septic patients, persistent positive daily fluid balance beyond day four is associated with higher mortality.[113]

In our study 16 of 42 (38%) patients, who were comatose at hospital admission, died within 180 days after OHCA. Six of these died within 48 hours due to circulatory shock and multi-organ failure. Removing these six patients from the analysis did not notably alter the described circulatory development.

Clinical phenotypes in PCAS

In paper I, we identified four clusters of similar circulatory trajectories after OHCA.
Three of the four clusters reached a finite state after 72 hours: either transferred to the ward in a circulatory stable condition ('Cluster 1') or dead ('Cluster 3' and 'Cluster 4'). 'Cluster 2' remained in intensive care during the study period. We found that initial shockable rhythm was significantly associated with a favorable circulatory trajectory, while metabolic acidosis at admission was associated with an unfavorable circulatory trajectory. Both non-shockable cardiac rhythm and metabolic acidosis are among identified predictors for increased cardiovascular support and mortality after OHCA.[53,95,114]

The majority of the patients who remained in the ICU (i.e. 'Cluster 2') had, according to their SOFA-scores, multi-organ failure. Still, 78% of these patients ultimately survived with good neurologic outcomes (CPC 1). In an effort to optimize treatment and improve prognostication and outcome, there is a growing interest in discovering more homogenous subgroups within a heterogeneous patient group.[93,115–117] In fact, unsupervised machine learning methods can be a valuable tool to identify new classifiers, including more complicated patterns, which may expand our knowledge about the clinical course and underling pathogenesis in PCAS.

In this study the trajectory analysis of the subgroups revealed that within 72 hours less than half of the patients still remained in the ICU, and the majority of these patients, although critically ill, survived with a good cerebral outcomes. Therefore, current practice with long-term intensive care treatments of OHCA patients seems indicated and meaningful.

The inflammatory response and its association with circulatory failure in PCAS

In paper II we found that longer time to ROSC and higher initial lactate level were associated with complement activation (TCC and C3bc), pro-inflammatory cytokines (IL-6 and IL-8) and markers of glycocalyx shedding (syndecan-1). In turn, the inflammatory response had a time-dependent circulatory pattern: Complement activation was initially associated with lower MAP, CO and SVR, and increased need of circulatory support, while pro-inflammatory cytokines showed a consistent association, and endothelial biomarkers a delayed association with the same circulatory patterns. This is in line with previous findings that IL-6 was consistently associated with vasopressor support, while thrombomodulin and syndecan-1 showed a delayed pattern.[45]

To our surprise, VE-cadherin, a marker for endothelial injury, was found in higher concentrations in less critically ill patients, but was also associated with improved circulatory variables and lower SOFA score. We have no explanation for this counterintuitive relationship.

High levels of TCC and IL-6 at admission were significantly associated with 30-days mortality. Previously, low levels of complement regulatory protein MAp19, high levels of complement C3bc and TCC, together with IL-6 have been shown to be associated with mortality after OHCA.[38,40,118,119]

Aspiration pneumonia is often an unavoidable part of cardiac arrest. Thus, it is conceivable that the inflammatory response we observed is a combination of ischemia and reperfusion injury, pneumonitis and infections. However, Oppert *et al.* found that the abrupt rise in acute phase proteins after cardiac arrest was similar in patients with and without infection.[120]

Characteristics of circulatory failure in PCAS

In paper III we found a significant increase in CPO, SW and SV during the first 48 hours in patients after OHCA. After 48 hours both the SW and CPO curves flatten, which could indicate a restored heart function.[121] Furthermore, the similarity between the SW and CPO curves indicates that the increase in CPO is not due to an increasing heart rate. Heart rate is affected by temperature, but lowering the body temperature to 36 °C seemed to only have a negligible bradycardic effect. In previous studies, reflexive sinus bradycardia during mild

hypothermia has been associated with increased survival after OHCA.[122,123] However, this result was not replicated in a recent study.[124] Although early hemodynamic measurements have not been consistently associated with outcome, a lack of improvement over time has been associated with increased mortality.[30,125] Observing this trend, Babini *et al.* proposed that preserved heart-rate variability, recovering cardiac output, and constant lactate clearance indicates a more "benign circulatory phenotype" after OHCA.[68] This is consistent with the observations in the current study.

In compliance with previous and current guidelines MAP were kept above 65 mmHg.[13,14] In the initial phase, this was achieved with fluid and noradrenaline infusion. Noradrenaline is the preferred vasoactive agent in PCAS.[14,126,127] Even if calculated Ea fell as a consequence of rising SV and stable blood pressure, this did not lead to an increase in fluid or noradrenaline infusions. We found a similar trend with CO and SVR in paper I. Falling vascular resistance without increasing vasopressor infusion, indicates that the physician viewed the clinical situation and tissue perfusion as adequate. This phenomenon, where decreasing vascular resistance does not lead to increased vasopressor doses, has been shown, but not emphasized, in previous studies.[128,129] Taken together, this demonstrate that a *calculated* low vascular resistance is not an exact measure of a clinical relevant vasoplegia in need of treatment.

We found a significantly longer time to noradrenaline discontinuation in patients with high pro-BNP concentrations. Pro-BNP is considered a marker for heart failure, and in line with the current belief we had expected that inflammatory biomarkers, such as IL-6 and syndecan-1, would be associated with longer need of circulatory support. Still, three studies have shown significantly higher levels of pro-BNP in non-survivors compared with survivors after OHCA. The level of increase and the strength of association with survival status, however, differed between the studies.[130–132]

Neumar *et al.* has described the clinical manifestations of systemic ischemia-reperfusion injury to include intravascular volume depletion, impaired vasoregulation, impaired oxygen delivery and utilization.[13] Impaired microcirculation is central to the circulatory pathogeneses in sepsis.[133,134] It is believed that systemic ischemia-reperfusion injury after OHCA induces a similar circulatory impairment.[31] Indeed, two small studies that used sidestream dark-field (SDF) imaging found initial reduced microcirculatory flow, which improved over the 24 hours after OHCA.[61,62] In the presence of an adequate DO_2, an increased $P(v\text{-}a)CO_2$ gap is

considered to be a sign of microcirculatory impairment, and for sepsis patients, it has been shown to correlate with reduced SDF-evaluated flow.[135] Reduced tissue perfusion is also associated with increased lactate levels. The lactataemia in circulatory shock is multifactorial. However, during shock it is now commonly regarded as a catecholamine-induced hyper-metabolism rather than a anaerobic metabolism.[136] Either way, lack of lactate clearance is a marker of sustained "metabolic stress", and associated with mortality in critically ill patients.[137] In our study, both lactate and $P(v\text{-}a)CO_2$ gap were normalized within 24 hours, which may indicate improved microcirculatory conditions.

Conclusion

In this observational cohort study we came to the following conclusions:

- The circulatory development over time in PCAS was characterized by an initial low oxygen delivery, cardiac output and cardiac power output, due to a low stroke volume and stroke work, which increased during the first 48 hours. Mean arterial pressure was kept stable above 65 mmHg with diminishing need for circulatory support. Therefore, calculated systemic vascular resistance and aortic elastance was correspondently initially high, and fell, without apparent clinical consequence.

- Non-shockable cardiac rhythm and low base excess at admission were associated with an unfavorable circulatory trajectory, whereas long time to ROSC and high lactate level at admission were associated with initially higher levels of pro-inflammatory biomarkers.

- High levels of TCC, C3bc, IL-6, IL-8 and syndecan-1 were in turn associated with reduced circulation and increased need of circulatory support, especially in the initial 48 hours. Patients that presented with high levels of TCC and IL-6 at admission had increased 30-days mortality.

- However, biomarkers indicating acute heart failure (pro-BNP), and not inflammation (IL-6, CRP and syndecan-1), were significantly associated with longer need of vasopressor support.

- Taken together, circumstantial evidence from this study does not support the idea that inflammatory vasodilatation in PCAS is late and emerging, but rather early and resolving, as both micro- and macrocirculatory homeostasis was mainly restored within 48 to 72 hours.

Future perspectives

Recently, a large RCT comparing hypothermia (33 °C) and normothermia (<37.8 °C) after OHCA was published and demonstrated no difference in mortality or neurologic disability.[3] Consequently, there is currently no specific treatment being offered patients with PCAS except ordinary intensive care.

Furthermore, no evidence exist to date showing that pharmacological modification of the immune response in critical illnesses can improve the outcome,[138] and it has been previously shown that hypothermia did not alter the inflammatory response after OHCA.[36] Still, both cytokine and complement inhibition might be a therapeutic approach in various inflammatory conditions related to ischemia-reperfusion injury.[2,139] For example tocilizumab, an IL-6 receptor blocker, has shown a promising effects on biomarker release after cardiac arrest.[140]

Different machine learning methods, such as cluster analysis, provide an effective tool in analyzing large volumes of data to find clinically relevant patterns. Future research, utilizing machine learning, might provide better understanding of the underling pathogenesis, generate new hypothesis and find clusters of similar patients that are more likely to benefit from specific therapies, and thus provide a more "personalized" treatment.

Personalized medicine, described as the careful matching of medical care with the patient's biology, has in practice been understood as the use of genetic information to optimize medications.[141] Genetically guided treatment is currently not feasible in critical care, and will probably remain an unrealistic utopia in the foreseeable future. However, the opposite, which is the "one-size-fits-all" guidelines of modern evidence based intensive care medicine, might be too crude to encompass all patients. Indeed, there is a worrisome failure to replicate scientific results in intensive care medicine.[142] Whether failure to replicate is caused by underpowered studies, or a result of including poorly characterized and heterogeneous patient groups, believed to be more similar than they really are, are debatable.[143–145] Santhakumaran *et al.* demonstrated heterogeneity of treatment effects in one of three ICU RCTs they re-analyzed.[146] Surely, it is conceivable that similar subgroup variation in benefit and harm exist in other populations as well. Recently, latent class analysis, a machine-learning method, was used to find subgroups with therapeutic response to corticosteroids in coronavirus disease 2019 related acute respiratory distress syndrome.[147] Thus, machine-learning methods, which

can utilize the information from the vital signs of clinical phenotypes and the molecular signature of hyper-inflammatory endotypes, are invaluable in identifying such subgroups of high-risk patients that might benefit from a different therapy. This might accelerate the transition to the more realistic "precision medicine" in critical care.[148]

Even without specific therapies, survival after cardiac arrest has improved slowly but steadily. This is probably due to subtle improvements in the "chain-of-survival", i.e. public recognition and response with bystander CPR, proximity to public automated defibrillators, ambulance response time, systematic and evidence-based intensive care medicine, and rehabilitation afterwards. Still, the elements in the "chain-of-survival" is not equally strong in all areas, and there is an unfortunate large socio-economic gradient, both between and within countries.[149] AHA recommend that patients should preferably be admitted to cardiac arrest centers that provide around-the-clock percutaneous coronary interventions, availability of advanced circulatory support (e.g. VAD or ECMO), an experienced ICU staff, and multidisciplinary collaboration in both the acute treatment, prognostication and rehabilitation.[150] Although this concept is usually informally accepted, it is not formally established due to both scarce recourses and geographical challenges.[151] However, this is already implemented for myocardial infarction, trauma and stroke that meet certain criteria, and I believe the same will happen in the treatment of OHCA.

Finally, I believe that a future improvement in cardiac arrest survival does not lie in one spectacular innovation, but rather in subtle continuous improvements in the treatment logistics of "precision medicine".

Keep calm and carry on.

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Papers I–III

"Science is simply common sense at its best, that is, rigidly accurate in observation, and merciless to fallacy in logic."

- Thomas Henry Huxley

Paper I

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RESEARCH Open Access

Circulatory trajectories after out-of-hospital cardiac arrest: a prospective cohort study

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Abstract

Background: Circulatory failure frequently occurs after out-of-hospital cardiac arrest (OHCA) and is part of post-cardiac arrest syndrome (PCAS). The aim of this study was to investigate circulatory disturbances in PCAS by assessing the circulatory trajectory during treatment in the intensive care unit (ICU).

Methods: This was a prospective single-center observational cohort study of patients after OHCA. Circulation was continuously and invasively monitored from the time of admission through the following five days. Every hour, patients were classified into one of three predefined circulatory states, yielding a longitudinal sequence of states for each patient. We used sequence analysis to describe the overall circulatory development and to identify clusters of patients with similar circulatory trajectories. We used ordered logistic regression to identify predictors for cluster membership.

Results: Among 71 patients admitted to the ICU after OHCA during the study period, 50 were included in the study. The overall circulatory development after OHCA was two-phased. Low cardiac output (CO) and high systemic vascular resistance (SVR) characterized the initial phase, whereas high CO and low SVR characterized the later phase. Most patients were stabilized with respect to circulatory state within 72 h after cardiac arrest. We identified four clusters of circulatory trajectories. Initial shockable cardiac rhythm was associated with a favorable circulatory trajectory, whereas low base excess at admission was associated with an unfavorable circulatory trajectory.

Conclusion: Circulatory failure after OHCA exhibits time-dependent characteristics. We identified four distinct circulatory trajectories and their characteristics. These findings may guide clinical support for circulatory failure after OHCA.

Trial registration: ClinicalTrials.gov: NCT02648061

Keywords: Out-of-hospital cardiac arrest, Post-cardiac arrest syndrome, Circulation, Hemodynamic, Cluster, Sequence analysis

Introduction

Circulatory failure frequently occurs after out-of-hospital cardiac arrest (OHCA) and is part of the post-cardiac arrest syndrome (PCAS). It is believed to be secondary to myocardial dysfunction and systemic inflammation due to global ischemia–reperfusion injury [1].

Three studies provided detailed descriptions of circulatory patterns in subgroups of OHCA patients by measuring cardiac output (CO) and systemic vascular resistance (SVR) at specific time points [2–4]. The circulatory instability was characterized by a low cardiac index and filling pressures, and the median time to onset was approximately seven hours [2]. After 24 h, the cardiac index increased, but superimposed vasodilatation delayed the discontinuation of vasopressors and fluid treatment [2].

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The American Heart Association (AHA) guidelines for resuscitation and post cardiac arrest treatment recommend tailoring treatment to the specific subgroups of patients who most likely benefit from the interventions [5]. Sequence analysis is a method to describe and analyze patient development over time and to identify clusters of patients with similar trajectories [6, 7]. Three cohort studies of patients with sepsis have utilized this method to identify patients with similar "clinical phenotypes" [8–10]. To date, no studies have used sequence analysis in patients after OHCA.

The International Liaison Committee on Resuscitation (ILCOR) indicates several knowledge gaps concerning the optimal treatment of PCAS. One of these knowledge gaps is how to best deliver circulatory support after cardiac arrest [11].

The aim of this study was to analyze circulatory development after OHCA. To better understand the different "circulatory phenotypes" in PCAS, we identified clusters of patients with similar trajectories and potential predictors for cluster membership.

Methods

Study design

This was a prospective single-center observational cohort study including patients with OHCA who were admitted to the hospital with return of spontaneous circulation (ROSC). Patients were included between January 2016 and November 2017.

Setting

St. Olav's University Hospital is a 938-bed tertiary hospital in Trondheim, Norway, serving a population of approximately 700,000 [12].

Eligibility

Both comatose and awake adults admitted to the ICU with ROSC after OHCA were assessed for eligibility. Exclusion criteria were age < 18 years, pregnancy, assumed septic or anaphylactic etiology of cardiac arrest, transfer from another hospital, decision to limit life-sustaining therapy upon arrival, acute cardiothoracic surgery, intervention with extracorporeal membranous oxygenation (ECMO) or a ventricular assist device (VAD) before arrival in the ICU.

Study period

Patients followed the study protocol from the time of admission and the subsequent five days, or until the patient died, underwent ECMO/VAD/acute cardiothoracic surgery, life-prolonging therapies were limited, or were transferred to a general ward or another hospital. Day zero had variable length depending on the time of inclusion, whereas day one started the following morning at 06:00.

Study procedure

All comatose patients without contraindications received a pulmonary artery catheter (PAC) (Swan-Ganz CCombo, Edwards Lifesciences, USA) for continuous central hemodynamic measurements. Twice daily, we calibrated the PAC oxygen saturation sensors and measured wedge pressure.

The electronic critical care management system (Picis CareSuite, Optum Inc., USA) recorded heart rate, blood pressure, peripheral transcutaneous oxygen saturation, fluid balance, medications and respiratory support. In patients with PAC, the system collected cardiac output, pulmonary artery pressure, mixed venous saturation, and calculated systemic vascular resistance. From the prehospital report and hospital record, we registered data according to the Utstein template [13], Charlson Comorbidity Index [14], and information on assessment and treatment.

We calculated the Simplified Acute Physiology Score 2 (SAPS-2) 24 h after admission and Sequential Organ Failure Assessment (SOFA) scores daily [15, 16]. After 30 and 180 days, we obtained survival status and cerebral performance category (CPC) from the hospital records [17].

Thrombocyte count and creatinine and bilirubin serum concentrations were measured at inclusion and every day at 06:00 during the study period. Every six hours, we obtained an arterial blood gas sample.

Post-cardiac arrest care and cardiovascular support

Comatose patients were cooled (36 °C) for 24 h. Patients with a suspected ischemic etiology of cardiac arrest received coronary angiography and percutaneous revascularization.

In the presence of hypotension and clinical signs of tissue hypoperfusion, circulation was optimized through fluid and vasopressor administration based on the department's guidelines on circulatory support. A detailed description of the post-cardiac arrest care in this study has been published [18].

Circulatory state classification

Patients' circulatory measurements were classified every hour into one of three circulatory states: 'undisturbed', 'disturbed' or 'severely disturbed', based upon the least favorable measurement. We used predefined values of mean blood pressure, heart rate, lactate concentrations, fluid resuscitation, vasoactive medications and the need for mechanical circulatory support (Table 1) [18]. There is no consensus on the definition or classification of circulatory instability. For this reason, hemodynamic variables

Table 1 Circulatory states[a]

Variables	Undisturbed	Disturbed	Severely disturbed
Mean arterial pressure, mmHg	≥ 65	45–64	< 45
Heart rate, beats per minute	51–100	< 50, 101–130	≤ 40, > 130
Lactate, mmol/l	< 2	2–4	> 4
Fluid resuscitation, l/hours	< 0.5	0.5–1.9	≥ 2
Norepinephrine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	< 0.1	0.1–0.29	≥ 0.3
Dobutamine, $\mu g \cdot kg^{-1} \cdot min^{-1}$	No	< 10	≥ 10
Vasopressin	No	No	Yes
Epinephrine	No	No	Yes
Levosimedan	No	No	Yes
Aorta balloon pump	No	No	Yes

[a] Every hour a patient was classified as having undisturbed, disturbed or severely disturbed circulation according to the least favorable measurement at that time (e.g., isolated mean arterial pressure of 40 mmHg is sufficient to classify a patient as having severely disturbed circulation)

and corresponding cutoff values were based upon general guidelines, clinical relevance and availability during routine monitoring of critically ill patients. Central venous oxygen saturation was initially included in the classification but was omitted because therapeutic infusions hindered sufficiently frequent measurements [18].

Statistical analysis

We assessed patients' transitions among the circulatory states of 'undisturbed', 'disturbed' or 'severely disturbed' using a multistate model [19]. For instance, a patient in a 'disturbed' state may transition to either an 'undisturbed' or 'severely disturbed' state [20]. Furthermore, the state transitions also describe a sequence of states, i.e., a "trajectory", for each patient. In addition, if the patient did not complete the study period, we considered the reason for incompletion to be informative and coded it into one of three "absorbing states", i.e., 'death', 'still treated in ICU' or 'transferred to ward in stable circulatory condition'.

We used sequence and cluster analysis to analyze patient trajectories. In this process, an algorithm uses pairwise optimal matching and Ward's minimal variance method to group the sequences hierarchically into clusters of similar trajectories [6]. In optimal matching, similarity between trajectories is measured by the penalty cost for editing a sequence into another, and the result of all pairwise matches is recorded in a matrix. As recommended, the penalty cost of insertion or deletion was set to 1, and the cost of substitution was based on the transition rate [6]. Ward's method evaluates all possible cluster combinations to build a hierarchy of clusters with the least variance bottom-up until the preset number of clusters is identified [6]. Based on previous studies on intensive care populations, we aimed to identify four clusters [9, 21].

We used ordered logistic regression to estimate the odds ratio for cluster membership based on independent factors related to patient demographics, resuscitation episode and status at hospital admission. In ordered logistic regression, the odds ratios among clusters are equal, and the odds ratio is interpreted as the odds of a higher (here: worse) cluster membership. Based on predictors from previous studies, we included age, comorbidity, shockable initial rhythm, time to ROSC, base deficit at admission and circulatory shock at admission to predict cluster membership and the anticipated circulatory trajectory [22, 23].

Data were extracted and analyzed using MATLAB software (Mathworks Inc., USA). Statistical analyses were performed using Stata version 16.0 (StataCorp LCC, USA) and R version 3.6.0 [24]. The R package "TraMineR" was used for sequence analysis and visualization of both individual sequences of circulatory states and transversal distributions of circulatory states during the ICU period [6].

Sample size

This is a descriptive study, and no formal sample size calculation was performed [25].

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics, Central Norway Health Region (REK Midt, No. 2015/1807) approved this study. Written informed consent was obtained from either the patient or next-of-kin if the patient was unable to consent.

Results

Demographics

Among 71 patients admitted with ROSC after OHCA during the study period, 65 were assessed for eligibility,

and 50, 42 of which were comatose, were included in the study (Supplementary Figure 1). Fifteen patients were excluded for the following reasons: seven because life-sustaining treatment was withdrawn upon arrival at the hospital, two had septic causes of cardiac arrest, two were not in need of intensive care treatment, two patients received VAD, one received ECMO and one patient underwent immediate cardiothoracic surgery. PAC was inserted in 30 of the included comatose patients. The primary contraindications were bleeding diastasis after percutaneous coronary intervention, implantable cardioverter-defibrillator or technical difficulties.

Baseline demographic data are presented in Table 2. Mean patient age was 62.7 (standard deviation (SD) 15.3) years, 40 (80%) were males, and the median Charlson Comorbidity Index score was 3 points (first to third quartiles (Q1–Q3): 2–4). In 42 (84%) patients, cardiac arrest was of cardiac etiology, and ventricular fibrillation was the initial rhythm in 37 (74%) patients. Forty-four (88%) patients received bystander cardiopulmonary resuscitation. The median ambulance response time was 9.5 (Q1–Q3: 5–13.5) minutes. ROSC was achieved after a median of 24 (Q1–Q3: 14–32) minutes from the time of the emergency call.

Clinical circulatory variables

The median mean arterial pressure (MAP) was stable at approximately 70 mmHg and increased slightly after 24 h, whereas the median heart rate varied between 70 and 80 beats per minute (Fig. 1A and B). Mean pulmonary artery wedge pressure was stable between 11 and 13 mmHg, whereas median mean pulmonary arterial pressure (MPAP) was stable between 23 and 25 mmHg. The initial median CO was 2.8 $L \cdot min^{-1}$, with a median SVR of 1400 $dynes \cdot sec^{-1} \cdot cm^{-5}$ (Fig. 1C and D). Thereafter, the median CO increased, and the median SVR decreased until 48 h, when the median CO stabilized at approximately 6 $L \cdot min^{-1}$ and the SVR stabilized at approximately 800 $dynes \cdot sec^{-1} \cdot cm^{-5}$. Fluid administration was highest from admission to the following morning, and by the fourth morning, the median fluid balance was negative (Fig. 1E). The mean noradrenaline dose was initially 0.08 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and decreased to 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during the study period (Fig. 1F).

Circulatory state sequences and distribution

During the study period, 869 circulatory state transitions were recorded and analyzed. One patient was excluded from this analysis due to problems with data sampling. The hourly distributions of patients in each circulatory state, together with patients who died or were transferred out of the ICU, are shown in Fig. 2.

At hospital admission, approximately half of the patients were in a state of 'severely disturbed' circulation. Over time, circulation improved for most patients (Fig. 2). More patients entered the state of 'disturbed' circulation during the first 72 h than after. At the end of the study period, 14 (28%) patients had been transferred to the ward, 23 (46%) were still in ICU care, and 12 (24%) died (Fig. 2).

Hypotension, heart rate and dose of noradrenaline were the variables that most frequently "triggered" a change to a worse circulatory state (Supplementary Figure 2).

Circulatory trajectories

We identified four typical clusters of circulatory trajectories after OHCA. 'Cluster 1' (28% of patients) describes a circulatory trajectory where most patients were stabilized within 48 h and transferred to a general ward (Fig. 3a). 'Cluster 2' was the dominant cluster (46% of patients) and showed a trajectory where the patients were mostly in the disturbed circulatory state and remained sedated and ventilated during the study period (Fig. 3b).

'Cluster 3' (8% of patients) describes a trajectory in predominantly disturbed circulatory states that ends in death within 96 h (Fig. 3c), whereas 'Cluster 4' (16% of patients) shows a more dramatic trajectory with patients in severe circulatory state until death, typically within 24 h (Fig. 3d).

In the multivariable analysis, base deficit at admission (OR 1.18 per $mmol \cdot L^{-1}$) was significantly associated with a less favorable cluster and thus a worse circulatory trajectory (Table 3). An initial shockable cardiac rhythm (ventricular fibrillation or tachycardia) was associated with a more favorable cluster (OR 0.07). Characteristics and sequence plots of the clusters are presented in Supplementary Table 1 and Supplementary Figure 3, respectively. The model did not violate the proportional odds assumption between the clusters ($X^2 = 0.15$).

Morbidity and mortality

During the first four days, the patients had median SOFA scores between 10 and 11 points, which improved on the fifth day to a median of 7.5 points. The most frequent organ system failures were circulatory, neurologic and respiratory (Supplementary Table 2).

Sixteen patients died within 180 days (Table 2). Six patients died within 48 h, predominantly from refractory circulatory shock or multiorgan failure (4 of 6 patients), while ten patients died later, mostly due to irreversible brain injury (8 of 10 patients). All eight patients who were awake at admission survived with good neurologic outcomes (defined as CPC 1). Twenty-two of the 26 patients who were comatose at admission and discharged alive from the hospital had good neurologic outcomes (CPC 1) after 180 days.

Table 2 Demographics and outcomes

Patient characteristics and outcomes	All *N* = 50	Comatose *n* = 42 (84%)	Awake *n* = 8 (16%)
Demographics			
Age, years, mean (sd)	62.7 (15.3)	64.8 (14.5)	51.8 (14.5)
Male sex, no. (%)	40 (80)	35 (83)	5 (62)
Body mass index, mean (sd)	27.5 (6.6)	27.7 (7)	26.4 (2.3)
Medical history			
Charlson comorbidity index, median (Q1–Q3)	3 (2–4)	3 (2–5)	2 (1–3)
Cerebral performance category, median (Q1–Q3)	1 (1–1)	1 (1–1)	1 (1–1)
Cardiac arrest			
Location, no. (%)			
Place of residence	19 (38)	16 (38)	3 (37)
Public place	21 (42)	16 (38)	5 (63)
Other	10 (20)	10 (24)	0 (0)
Bystander witnessed, no. (%)	42 (84)	34 (80)	8 (100)
Bystander performed CPR, no. (%)	44 (88)	37 (88)	7 (87)
First monitored rhythm, no. (%)			
Shockable			
Ventricular fibrillation	37 (74)	30 (71)	7 (88)
Ventricular tachycardia	2 (4)	1 (2)	1 (12)
Nonshockable			
Asystole	4 (8)	4 (10)	0 (0)
Pulseless electric activity	7 (14)	7 (17)	0 (0)
Number of defibrillations, median (Q1–Q3)	2 (1–4)	2 (1–4)	1 (1–2)
Time from cardiac arrest to event, median (Q1–Q3)			
Start of basic life support—min	1 (1–2)	1 (1–2)	1 (1–2)
Start of advanced life support—min	9 (5–13)	10 (5–15)	5 (2–7)
Return of spontaneous circulation—min	24 (14–32)	26 (19–35)	8 (4–14)
Adrenaline—mg, median (Q1–Q3)	0 (0–2)	1 (0–3)	0 (0–0)
Presumed etiology, no. (%)			
Cardiac	42 (84)	34 (81)	8 (100)
Asphyxia	5 (10)	5 (12)	0 (0)
Other	3 (6)	3 (7)	0 (0)
Certain pulmonary aspiration, no. (%)	9 (18)	9 (21)	0 (0)
At admission			
Body temperature, ℃, mean (sd)	35.3 (1.1)	35.2 (1.0)	36.5 (0.6)
In circulatory shock[a], no. (%)	18 (36)	18 (42)	0 (0)
Arterial blood gas, mean (sd)			
pH	7.18 (0.14)	7.17 (0.15)	7.28 (0.05)
pCO_2, kPa	6.2 (1.8)	6.4 (1.9)	5.2 (0.7)
Base excess, mmol/l	-9.4 (7.4)	-9.7 (7.7)	-7.6 (5.2)
HCO_3, mmol/l	17.9 (4.5)	17.7 (4.4)	19.1 (4.7)
Lactate, mmol/l	6.7 (4.2)	6.9 (4.5)	5.9 (2.7)
Oxygen saturation, %	92.1 (9.4)	91.5 (10.1)	95.2 (3.1)
Acute intervention, no. (%)			
Angiography	26 (52)	21 (50)	5 (63)
Percutaneous coronary intervention	21 (42)	17 (40)	4 (50)
Computer tomography scan	18 (36)	16 (38)	2 (25)
Pulmonary artery catheter	30 (60)	30 (71)	0 (0)
Therapeutic hypothermia protocol initiated	28 (56)	28 (67)	0 (0)

Table 2 (continued)

Patient characteristics and outcomes	All *N* = 50	Comatose *n* = 42 (84%)	Awake *n* = 8 (16%)
Prone position, no. (%)	2 (4)	2 (5)	0 (0)
Simplified Acute Physiology Score II [b], mean (sd)	62 (19)	68 (12)	28 (9)
Length of stay			
ICU, days, median (Q1–Q3)	6 (3–12)	8 (4–12)	2 (2–3)
Ventilator time, hours, median (Q1–Q3)	64 (12–162)	93 (28–173)	0 (0–0)
Hospital, days, median (Q1–Q3)	14 (7–20)	14,5 (7–20)	13 (6–16)
Outcome, 180 days			
Mortality, n (%)	16 (32)	16 (38)	0 (0)
Cerebral	10 (20)	10 (23)	-
Circulatory	2 (4)	2 (5)	-
Respiratory	0 (0)	0 (0)	-
Multiorgan failure [c]	3 (6)	3 (7)	-
Other/unknown	1 (2)	1 (2)	-
Cerebral performance category, n (%)			
I—Normal	22 (44)	22 (52)	8 (100)
II—Moderate disability	2 (4)	2 (5)	0 (0)
III—Severe disability	2 (4)	2 (5)	0 (0)
IV—Coma or vegetative state	0 (0)	0 (0)	0 (0)
V—Brain death	16 (32)	16 (38)	0 (0)

Comatose indicates patients who were intubated and gave no contact (GCS < 8). Awake patients were responsive and followed instructions

ICU Intensive care unit, *GCS* Glasgow coma scale, *SD* Standard deviation, *Q1–Q3* first to third quartiles

[a] Systolic blood pressure < 90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure > 90 mmHg

[b] After 24 h

[c] If failure of two or more organ systems led to death

Discussion

We found that after out-of-hospital cardiac arrest, patients had an overall two-phase circulatory development. Low CO and high SVR characterized the initial phase, whereas high CO and low SVR characterized the later phase. We identified four clusters of circulatory trajectories after OHCA. Multivariable analysis revealed that initial shockable rhythm was significantly associated with a favorable circulatory trajectory, while metabolic acidosis at admission was associated with an unfavorable circulatory trajectory.

Current AHA guidelines recommend MAP > 65 mmHg [5]. Patients included in our study had a median MAP between 70 and 75 mmHg during the study period. This was achieved by fluid and vasopressor administration. After liberal fluid resuscitation for the first 12 h, the need for fluids was gradually reduced in the following days. A similar pattern was evident for norepinephrine, where the mean dose was reduced after a few hours of intensive care. During the first 48 h, the CO increased concomitantly with a decrease in the calculated SVR. This pattern has previously been interpreted as resolving myocardial stunning, followed by peripheral vasodilatation due to systemic inflammation [2]. However, in this study, the median MAP and filling pressure were stable in the higher normal range, and the decrease in median SVR did not lead to an increase in vasopressor support or fluid resuscitation. Because CO and SVR are reciprocal values given constant arterial to venous pressure differences, the reduced calculated SVR might not be clinically relevant but rather an artifact due to increasing CO.

Seventy-two hours was found to be a "turning point" in circulatory stabilization. First, the majority of patients had reached a state of 'undisturbed' circulation by this time. Second, the majority of patients in this study achieved negative daily fluid balance between 72 and 96 h after cardiac arrest. In critically ill patients, persistent positive daily fluid balance beyond day four is associated with higher mortality [26, 27]. These observations suggest a stabilizing circulatory status within three days and are in accordance with findings by Laurent and coworkers [2].

We identified four clusters of circulatory trajectories. Three of the four clusters reached a finite state after 72 h: either stable and transferred to the ward ('Cluster 1') or dead ('Cluster 3' and 'Cluster 4'). 'Cluster 2' remained in intensive care after 72 h. SOFA scores showed that most

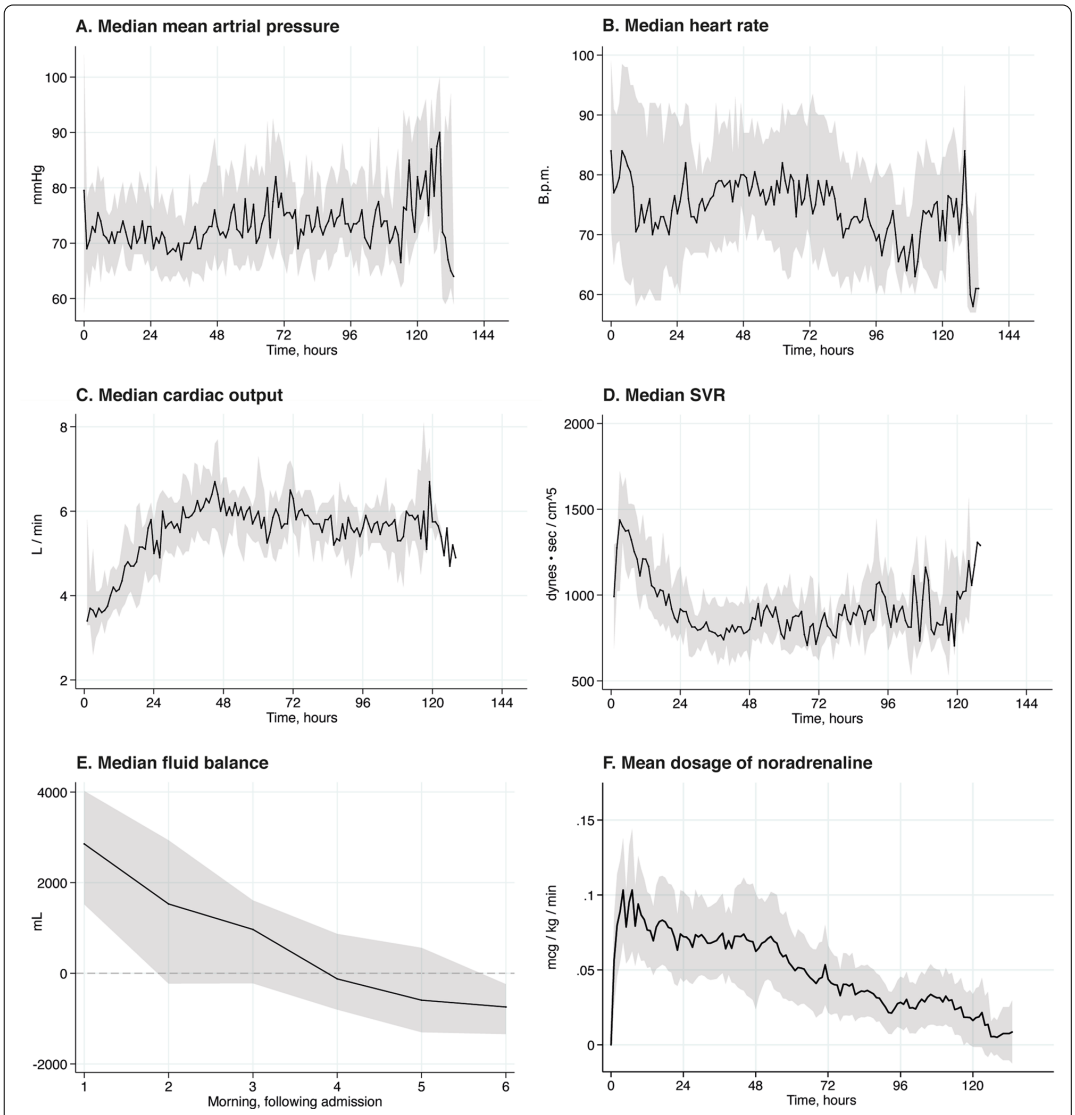

Fig. 1 Clinical circulatory variables. **A** Median value of the mean arterial pressure with interquartile range indicated by the shaded area. **B** Median heart rate with interquartile range indicated by the shaded area. **C** Median cardiac output with interquartile range indicated by the shaded area. **D** Median systemic vascular resistance with interquartile range indicated by the shaded area. **E** Median fluid balance with interquartile range indicated by the shaded area. Fluid balance was calculated every morning. **F** Mean dose of noradrenaline with 95% confidence interval indicated by the shaded area. B.p.m: beats per minute. SVR: Systemic vascular resistance

patients who remained in the ICU experienced multiorgan failure. However, 20 of 23 patients in 'Cluster 2' ultimately survived, and 18 of 23 patients had good neurologic outcomes (CPC 1). This observation supports that long-term intensive care treatment of OHCA patients is usually indicated, as the majority of patients, although critically ill, survived with a good cerebral outcomes.

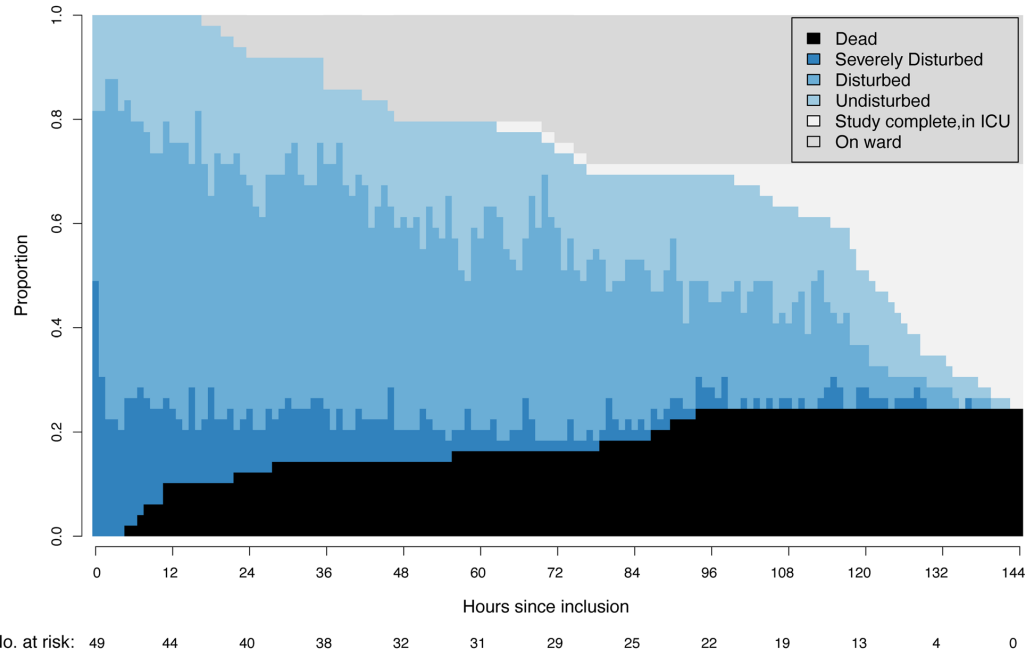

Fig. 2 Distribution plot. Hourly distribution of circulatory states, including number at risk for state transition and coded absorbing states (i.e., death, discharge to the ward and still in the ICU but out of study). ICU: Intensive care unit

Base deficit at admission was associated with an unfavorable circulatory trajectory, whereas initial shockable cardiac rhythm was associated with a favorable circulatory trajectory. Time to ROSC is a strong predictor for outcome [22], as seen in the univariable analysis. However, there is a high degree of collinearity between the initial shockable cardiac rhythm (i.e., ventricular tachycardia or fibrillation) and time to ROSC, and only the former was included in the final multivariable model [28, 29]. Bro-Jeppesen and coworkers have shown that increased lactate at admission is a strong predictor of vasopressor need [23]. This observation agrees with our findings, as both high lactate and metabolic acidosis at admission are indicative of "stressed metabolism" during the prehospital phase. Signs of stressed metabolism in combination with nonshockable rhythm, alternatively long time to ROSC, are suggestive of a high "ischemia–reperfusion burden" and thus a worse circulatory trajectory.

To make the result more clinically generalizable and to have a larger variability in independent predictors, thereby increasing the potential for identifying potential predictors, we included both awake and comatose patients. Awake patients usually experienced cardiac arrest, a short time to ROSC and excellent outcomes after hospital admission.

Age and comorbidities are usually associated with organ failure and mortality in an intensive care population [30] but were not significantly associated with a less favorable circulatory trajectory in our study. We observed a similar pattern of organ failure after OHCA as described by Roberts et al., with severe circulatory, respiratory and cerebral failures (SOFA score 3–4) and milder coagulation and kidney dysfunctions (SOFA score 1–2) [31]. Liver dysfunction was rare.

Sixteen of 42 (38%) patients who were comatose at hospital admission died within 180 days after OHCA. This is in line with previously reported mortality rates [32]. Furthermore, we found the same two-phase death pattern as previously described [33]; the early deaths were dominated by circulatory collapse and multiorgan failure, whereas later deaths were dominated by severe brain injury.

Strengths and limitations

The strengths of this study are its prospective design, consecutive inclusion of patients, and data including central hemodynamic measurements being obtained

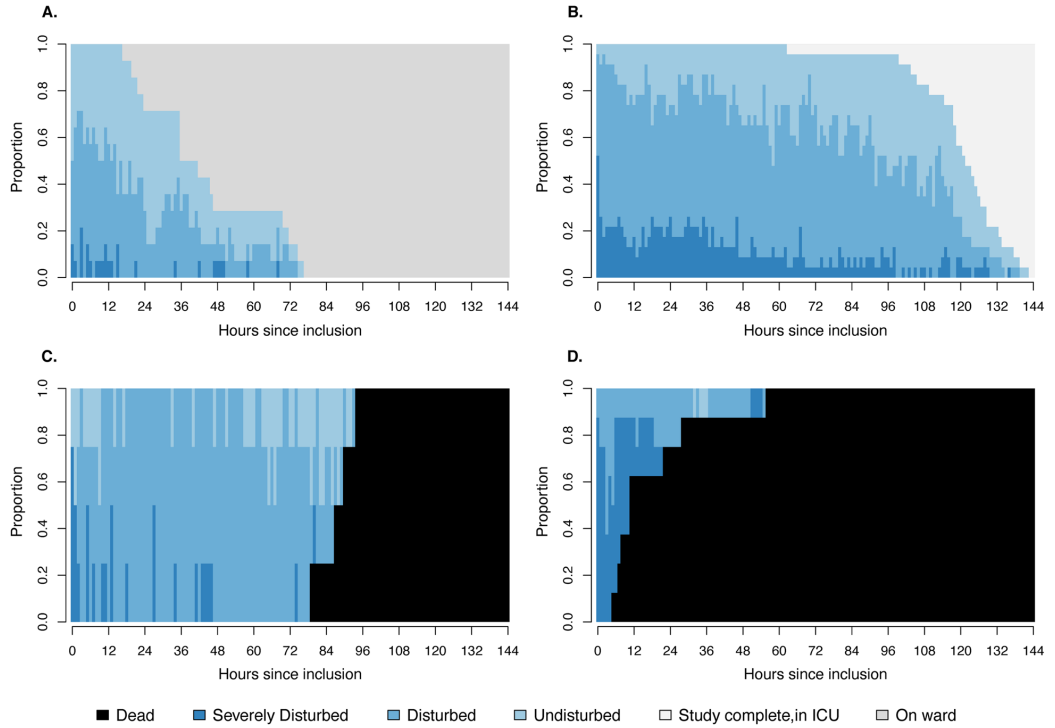

Fig. 3 Distribution plot for clusters 1 to 4. Hourly distribution of circulatory states, including death, discharge to the ward and still in the ICU but out of study. **A** Cluster 1. **B** Cluster 2. **C** Cluster 3. **D** Cluster 4. ICU: Intensive care unit

Table 3 Ordered logistic regression analysis of the association between cluster membership and demographic variables

Demographic variables	Univariable analysis Odds ratio (95% CI)	Multivariable analysis Odds ratio (95% CI)
Age, per 5 years	1.06 (0.88—1.28)	1.17 (0.84—1.63)
Charlson Comorbidity Index, point	0.97 (0.76—1.23)	1.06 (0.70—1.61)
Initial shockable rhythm, yes	0.02 (0.004—0.14)	0.07 (0.01—0.46)
Time to ROSC, per 5 min	1.04 (1.01—1.09)	1.12 (0.88—1.42)
Base deficit at admission, per mmol/L	1.23 (1.10—1.37)	1.18 (1.03—1.35)
Circulatory shock[a] in the ER, yes	5.64 (1.71—18.62)	1.93 (0.47—7.85)

In ordered logistic regression, the odds ratios among clusters are equal, and the odds ratio should be interpreted as the odds of a higher cluster than the compared cluster when the explanatory variable is increased by one unit and all other variables are held constant. Pseudo $R^2 = 0.30$

CI Confidence interval, *ER* Emergency room, *ROSC* Return of spontaneous circulation

[a] Systolic blood pressure < 90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure > 90 mmHg

continuously and frequently. We also recognize some potential limitations. First, this was a single-center study with a limited number of patients, which might limit the generalizability of the results and increase the probability of making a type-2 error. However, the number of circulatory state transitions was high (869 transitions) and was sufficient to perform analyses regarding circulatory trajectories. Second, the variables and thresholds used to

define the circulatory categories have not been validated. However, no consensus exists on how to define circulatory instability; therefore, we utilized measurements that are routinely available in ICU patients and thresholds based on general guidelines. Finally, sequence analysis is a complex procedure. The penalty cost of sequence editing is debatable, and a different value could have resulted in a different pairwise matching and perhaps cluster membership. However, the four clusters described in this study seem clinically reasonable.

Conclusions

Low CO and high SVR characterized the initial circulatory failure after OHCA. During the first 48 h, this pattern reversed to a high CO and low SVR. The majority of patients experienced circulatory stabilization within 72 h after cardiac arrest. We identified four clusters of patients with different severities of circulatory failure. Initial shockable cardiac rhythm was associated with a favorable circulatory trajectory, and low base excess at admission was associated with an unfavorable circulatory trajectory.

Abbreviations

AHA: American Heart Association; CA: Cardiac arrest; CO: Cardiac output; CPC: Cerebral performance category; ECMO: Extracorporeal membranous oxygenation; ICU: Intensive care unit; ILCOR: International Liaison Committee on Resuscitation; MAP: Mean arterial pressure; MPAP: Mean pulmonary arterial pressure; OHCA: Out-of-hospital cardiac arrest; PAC: Pulmonary artery catheter; PCAS: Post-cardiac arrest syndrome; ROSC: Return of spontaneous circulation; SAPS-2: Simplified Acute Physiology Score 2; SD: Standard deviations; SOFA: Sequential Organ Failure Assessment; SVR: Systemic vascular resistance; VAD: Ventricular assist device; Q1–Q3: First to third quartiles.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-021-01434-2.

Additional file 1: Supplementary Figure 1. Flowchart summarizing patient enrollment and exclusion. CA: Cardiac arrest. ICU: Intensive care unit. ECMO: Extracorporeal membranous oxygenation. OHCA: Out-of-hospital cardiac arrest. PAC: Pulmonary artery catheter. VAD: Ventricular assist device.

Additional file 2: Supplementary Figure 2. Heat-map showing which of the variables in the circulatory state model that categorizes the patient in a worse circulatory state. IABP: Intra-aortic balloon pump. MAP: Mean arterial pressure.

Additional file 3: Supplementary Figure 3. Sequence plot for cluster 1 to 4, showing sequences of longitudinal succession of circulatory states, i.e. trajectory, for every patient in the respective cluster. **A.** Cluster 1. **B.** Cluster 2. **C.** Cluster 3. **D.** Cluster 4. ICU: Intensive care unit.

Additional file 4: Supplementary Table 1. Demographic and mortality for cluster 1 to 4. * Systolic blood pressure <90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg. † Comatose were patients that were intubated and gave no contact (GCS <8). ER: Emergency room. GCS: Glasgow coma scale. ROSC: Return of spontaneous circulation. SD: Standard deviation. SAPS: Simplified Acute Physiology Score.

Additional file 5: Supplementary Table 2. Sequential Organ Failure Assessment score. * In sedated patients daily Glasgow Coma Scale is based on pre-sedation score. SOFA: Sequential Organ Failure Assessment. Q1–Q3: first to third quartiles.

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Authors' contributions

HL, DB, NKS and PK included patients, initiated treatment and placed all pulmonary artery catheters in accordance with the study protocol. HL, DB, NKS, PK, TS and KB supervised the study and patient care daily. ØG retrieved all patient files from the electronic critical care management system. HL, ML and TN contributed extensively to the statistical analysis. All authors contributed to interpreting the data and writing the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics, Central Norway Health Region (REK Midt, No. 2015/1807) approved this study. Written informed consent was obtained from either the patient or next-of-kin if the patient was unable to consent. This study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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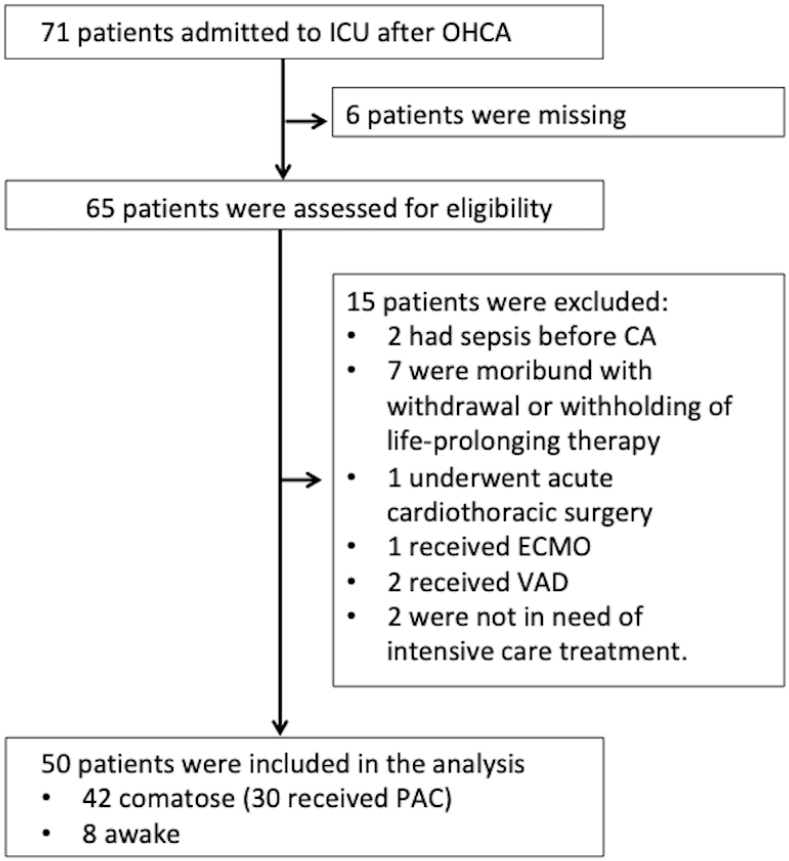
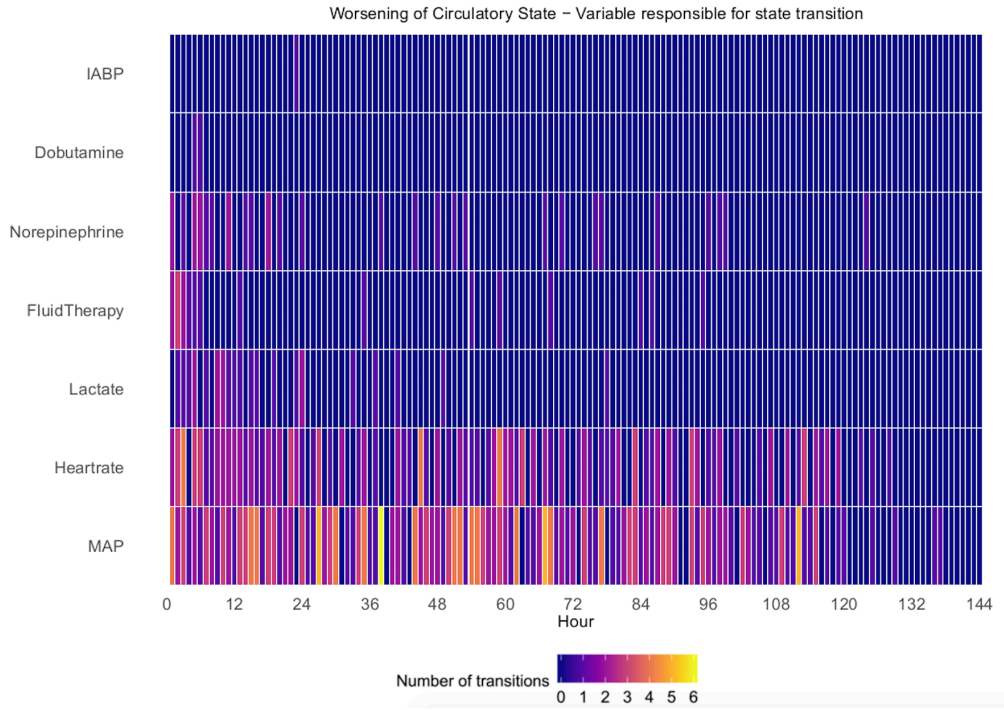
Publisher's Note

Supplementary Material

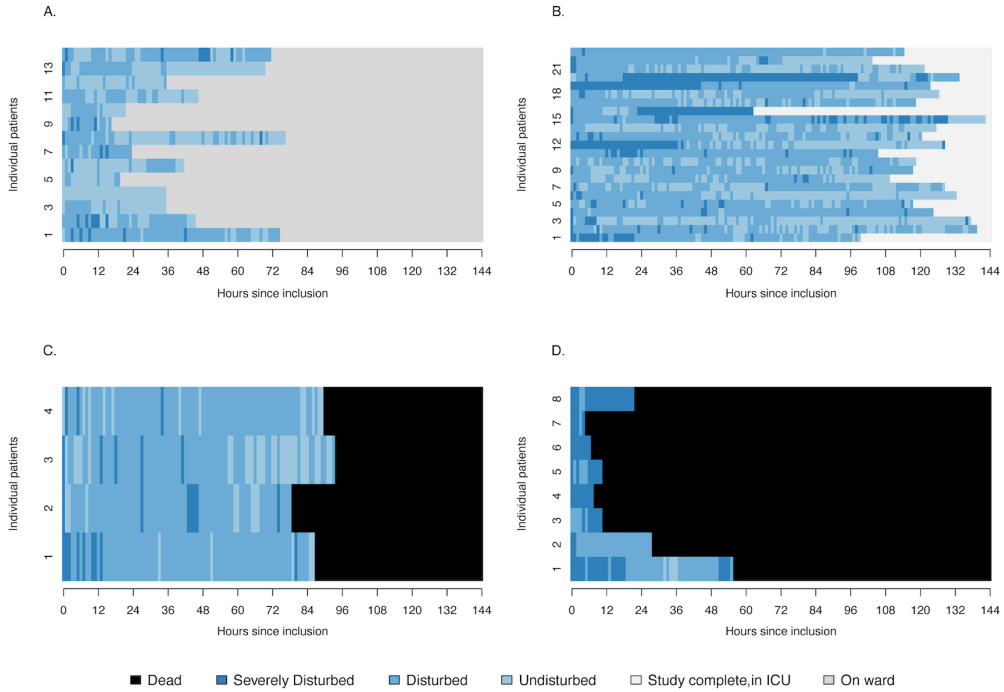
Langeland H, Bergum D, Nordseth T, Løberg M, Skaug TR, Bjørnstad K, Gundersen Ø, Skjærvold NK and Klepstad P. Circulatory trajectories after out-of-hospital cardiac arrest: a prospective cohort study. BMC Anesthesiology. 2021;21(1):219.



Supplementary Figure 1. Flowchart summarizing patient enrollment and exclusion.
CA: Cardiac arrest. ICU: Intensive care unit. ECMO: Extracorporeal membranous oxygenation. OHCA: Out-of-hospital cardiac arrest. PAC: Pulmonary artery catheter. VAD: Ventricular assist device.



Supplementary Figure 2. Heat-map.
Heat-map showing which of the variables in the circulatory state model that categorizes the patient in a worse circulatory state.
IABP: Intra-aortic balloon pump. MAP: Mean arterial pressure.



Supplementary Figure 3. Sequence plot.
Sequence plot for cluster 1 to 4, showing sequences of longitudinal succession of circulatory states, i.e. trajectory, for every patient in the respective cluster. **A.** Cluster 1. **B.** Cluster 2. **C.** Cluster 3. **D.** Cluster 4.
ICU: Intensive care unit.

Supplementary Table 1. Demographic and outcome for cluster 1 to 4.

Characteristics of clusters	1	2	3	4	ANOVA*	
	n = 14 (28%)	n = 23 (46%)	n = 4 (8%)	n = 8 (16%)	*F*	*p*
Age, years, mean (sd)	59 (16)	65 (12)	59 (13)	64 (21)	0.46	0.70
Body mass index, mean (sd)	26.4 (2.5)	27.3 (4.8)	34.3 (18.7)	25.6 (4.2)	1.73	0.17
Charlson comorbidity index, mean (sd)	3.5 (3.2)	3.5 (1.7)	2.7 (1.7)	3.5 (2.6)	0.13	0.94
Shockable initial rhythm, no. (%)	13 (92)	22 (95)	2 (50)	1 (12)	19.0	0.00†
Time to ROSC, min., mean (sd)	17.3 (11.4)	27.8 (15.8)	31.5 (6.13)	31.8 (19)	19.0	0.00†
Presumed cardiac etiology, no. (%)	13 (92)	22 (95)	3 (75)	3 (37.5)	7.2	0.00‡
Circulatory shock in the ER§, no. (%)	1 (8)	10 (43)	1 (25)	6 (75)	4.3	0.01¶
Comatose at admission**, no. (%)	7 (50)	23 (100)	4 (100)	8 (100)	10.7	0.00††
Initial pH, mean (sd)	7.3 (0.07)	7.18 (0.14)	7.08 (0.07)	7.06 (0.16)	6.3	0.00‡‡
Initial base excess, mmol/L, mean (sd)	-6.8 (4.8)	-9.3 (5.2)	-16 (2.8)	-16.3 (5.9)	7.6	0.00§§
Initial lactate level, mmol/L, mean (sd)	4.8 (3.3)	5.4 (3.4)	10.9 (1.1)	11.6 (4.1)	9.9	0.00†
SAPS II, mean (sd)	42.5 (17.3)	68.3 (11.2)	60 (3.1)	78.6 (13.3)	9.9	0.00†
30 days mortality, no. (%)	0 (0)	3 (13)	4 (100)	8 (100)	44.8	0.00†
180 days mortality, no. (%)	1 (7)	3 (13)	4 (100)	8 (100)	30.1	0.00†

* If one-way ANOVA indicated a significant difference between groups, Tukey's method were used to determine which of the groups that were significantly different.
† Cluster 3 and 4 is significantly different from cluster 1 and 2.
‡ Cluster 4 is significantly different from cluster 1 and 2.
§ Systolic blood pressure <90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.
¶ Cluster 4 and 1 are significantly different.
** Glasgow coma scale <8 and intubated.
†† Cluster 1 is significantly different from all other clusters.
‡‡ Cluster 1 is significantly different from cluster 3 and 4.
§§ Cluster 4 is significantly different from cluster 1 and 2, and cluster 3 is significantly different from cluster 1.
ER: Emergency room. ROSC: Return of spontaneous circulation. SD: Standard deviation. SAPS: Simplified Acute Physiology Score

Supplementary Table 2. Sequential Organ Failure Assessment

Organ failure	Day 1 n = 50	Day 2 n = 44	Day 3 n = 35	Day 4 n = 29	Day 5 n = 24
Total score, median (Q1–Q3)	11 (9-12)	10 (7-12)	11 (7-12)	10 (7-12)	10 (6-11)
Respiratory score, median (Q1–Q3)	3 (2-4)	2 (2-3)	3 (2-3)	2 (2-3)	2,5 (2-3)
Dysfunction (SOFA score 1 - 2), no. (%)	15 (30)	20 (45)	14 (40)	15 (52)	12 (50)
Failure (SOFA score 3 - 4), no. (%)	31 (62)	21 (49)	20 (57)	13 (44)	12 (50)
Circulatory score, median (Q1–Q3)	4 (3-4)	4 (3-4)	3 (0-4)	3 (1-3)	3 (0,5-3)
Dysfunction (SOFA score 1 - 2), no. (%)	3 (6)	1 (2)	2 (6)	3 (10)	5 (21)
Failure (SOFA score 3 - 4), no. (%)	42 (84)	37 (84)	24 (68)	19 (65)	13 (54)
Hepatic score, median (Q1–Q3)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Dysfunction (SOFA score 1 - 2), no. (%)	5 (10)	5 (11)	7 (20)	7 (24)	4 (16)
Failure (SOFA score 3 - 4), no. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Renal score, median (Q1–Q3)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)
Dysfunction (SOFA score 1 - 2), no. (%)	17 (34)	15 (34)	11 (32)	5 (17)	3 (12)
Failure (SOFA score 3 - 4), no. (%)	0 (0)	0 (0)	1 (3)	2 (7)	2 (8)
Coagulation score, median (Q1–Q3)	0 (0-0)	0 (0-0.5)	1 (0-1)	1 (0-1)	1 (0-1)
Dysfunction (SOFA score 1 - 2), no. (%)	3 (6)	11 (25)	20 (57)	16 (55)	16 (66)
Failure (SOFA score 3 - 4), no. (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cerebral score*, median (Q1–Q3)	4 (4-4)	4 (1-4)	4 (3-4)	4 (3-4)	4 (2-4)
Dysfunction (SOFA score 1 - 2), no. (%)	5 (10)	5 (11)	4 (11)	6 (21)	6 (25)
Failure (SOFA score 3 - 4), no. (%)	43 (86)	32 (72)	27 (78)	22 (75)	16 (66)

* In sedated patients daily Glasgow Coma Scale is based on pre-sedation score.
SOFA: Sequential Organ Failure Assessment. Q1–Q3: first to third quartiles.

Paper II

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Clinical paper

The inflammatory response is related to circulatory failure after out-of-hospital cardiac arrest: A prospective cohort study

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Abbreviations: C3bc, complement 3 activation product, CO, cardiac output, CRP, c-reactive protein, BFGF, basic fibroblast growth factor, ECMO, extracorporeal membranous oxygenation, ICAM-1, intercellular adhesion molecule 1, ICU, intensive care unit, IFNγ, interferon gamma, IL, interleukin, IP-10, interferon-inducible protein 10, MAP, mean arterial blood pressure, mCPIS, modified Clinical Pneumonia Infection Score, MIP-1β, macrophage inflammatory protein 1 beta, OHCA, out-of-hospital cardiac arrest, PCAS, post-cardiac arrest syndrome, PDGF-BB, platelet derived growth factor-BB, Q1–Q3, first to third quartile, RANTES, regulated on activation normal *T*-cell expressed and secreted, ROSC, return of spontaneous circulation, SOFA, sequential organ failure assessment, SVR, systemic vascular resistance, TCC, terminal C5b-9 complement complex, TNF, tumor necrosis factor, VAD, ventricular assist device, VCAM-1, vascular cell adhesion molecule 1, vWF, von Willebrand factor

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Abstract

Background: Whole body ischemia and reperfusion injury after cardiac arrest leads to the massive inflammation clinically manifested in the post-cardiac arrest syndrome. Previous studies on the inflammatory eect on circulatory failure after cardiac arrest have either investigated a selected patient group or a limited part of the inflammatory mechanisms. We examined the association between cardiac arrest characteristics and inflammatory biomarkers, and between inflammatory biomarkers and circulatory failure after cardiac arrest, in an unselected patient cohort.

Methods: This was a prospective study of 50 consecutive patients with out-of-hospital cardiac arrest. Circulation was invasively monitored from admission until day five, whereas inflammatory biomarkers, i.e. complement activation, cytokines and endothelial injury, were measured daily. We identified predictors for an increased inflammatory response, and associations between the inflammatory response and circulatory failure.

Results: We found a marked and broad inflammatory response in patients after cardiac arrest, which was associated with clinical outcome. Long time to return of spontaneous circulation and high lactate level at admission were associated with increased complement activation (TCC and C3bc), pro-inflammatory cytokines (IL-6, IL-8) and endothelial injury (syndecan-1) at admission. These biomarkers were in turn significantly associated with lower mean arterial blood pressure, lower cardiac output and lower systemic vascular resistance, and increased need of circulatory support in the initial phase. High levels of TCC and IL-6 at admission were significantly associated with increased 30-days mortality.

Conclusion: Inflammatory biomarkers, including complement activation, cytokines and endothelial injury, were associated with increased circulatory failure in the initial period after cardiac arrest.

Keywords: Post-cardiac arrest syndrome, Out-of-hospital cardiac arrest, Inflammation, Biomarkers, Haemodynamic

Introduction

The inflammatory response after out-of-hospital cardiac arrest (OHCA) share many characteristics with sepsis, and is therefore described as a "sepsis-like syndrome".[1] Whole body ischemia and subsequent reperfusion injury leads to a systemic inflammation, which is, together with anoxic brain injury and myocardial dysfunction, the main elements of the post-cardiac arrest syndrome (PCAS).[2]

The balance between pro- and anti-inflammatory cytokine signalling is important for the effect of the immune system on the development of organ failure.[3] Consequently, several studies have explored the role of cytokines as biomarkers for severity, risk of organ failure and mortality in sepsis.[4] Comparatively, few studies have evaluated the complement and cytokine response in PCAS, and most evidence stems from one large trial on targeted temperature management after cardiac arrest. Findings so far indicate that high levels of interleukin 6 (IL-6) and complement factor 3 were associated with mortality, whereas high levels of IL-6 and IL-10 were associated with organ failure.[1,5–9]

PCAS is characterized by a respiratory, neurologic and circulatory failure, but only mild affection of the liver, coagulation and kidneys.[10] The circulatory failure in PCAS is currently suggested to be two-phased; first, acute myocardial stunning that is followed by superimposed vasodilatation.[11] In a study of how endothelial and inflammatory responses affect the haemodynamic in PCAS, only IL-6 was associated with vasopressor support.[12] Other studies have observed that high levels of thrombomodulin, a marker for endothelial dysfunction, is associated with multi-organ failure in PCAS.[13–15] However, some of these studies excluded patients in circulatory shock at admission and some did not examine circulatory variables in detail. Thus, our investigation, which includes patients in circulatory shock, and gives detailed information on circulatory support together with central hemodynamic variables, is warranted.

The aim of this study was to investigate the inflammatory response, including complement activation, cytokine release and endothelial biomarkers, after OHCA, and its association with circulatory failure in PCAS.

Methods

Study design

This was a pre-planned analysis of a larger prospective, observational study of 50 patients admitted to hospital with return of spontaneous circulation (ROSC) after OHCA.[16] Hemodynamic variables have been published previously.[17] Patients were included between January 2016 and November 2017.

Setting and eligibility

St. Olav's University Hospital is a 938-bed tertiary hospital in Trondheim, Norway, serving a population of ~700,000. Both comatose and awake adults admitted to the ICU with obtained ROSC after OHCA were assessed for eligibility. Exclusion criteria were age <18 years, pregnancy, assumed septic or anaphylactic aetiology of cardiac arrest, transferal from other hospitals, decision to limit life-sustaining therapy upon arrival, or acute cardiothoracic surgery, intervention with extracorporeal membranous oxygenation (ECMO) or a ventricular assist device (VAD) before arrival at the ICU.

Study procedure

Patients followed the study protocol from time of admission and the following five days, or until one of the following events occurred: the patient died; treatment with ECMO or VAD was initiated; acute cardiothoracic surgery; life-prolonging therapies were withheld; the patient was transferred to a general ward or to another hospital. The day of admission (day zero) had variable length depending on the time of inclusion, whereas day one started the following morning at 06:00.

All comatose patients, without contraindications, received a pulmonary artery catheter (Swan-Ganz CCOmbo, Edwards Lifesciences, USA) for continuous central hemodynamic measurements. All circulatory variables and drug dosages were collected from the electronic critical care information system (Picis CareSuite, Optum Inc., USA). For circulatory variables we calculated the mean value over the period starting 30 min before and ending 30 min after each blood sample collection. From the pre-hospital report and hospital record, we obtained data according to the Utstein cardiac arrest tem-

plate,[18] Charlson Comorbidity Index,[19] and clinical information on assessment and treatment.

We calculated modified Clinical Pneumonia Infection Score (mCPIS) and Sequential Organ Failure Assessment (SOFA) scores daily.[20,21] After 30 days, we obtained vital status from the medical records.

Inflammatory biomarkers

Blood sampling and plasma preparation

Blood samples were drawn at inclusion and thereafter every morning during the ICU period. After gentle mixing, the blood samples were placed vertical for 30 min in ambient temperature, and then centrifuged at 2200*g* for 10 min. EDTA-plasma was frozen to –80 °C within 1 h from sampling. C-reactive protein (CRP) and haptoglobin were analysed together with the routine blood samples drawn in the ICU.

Complement activation

Complement activation, both initial C3 activation product (C3bc) and terminal C5b-9 complement complex (TCC), was measured by ELISA, using the Complement International Standard #2.[22]

Cytokines

Plasma levels of the following inflammatory cytokines, including interleukins, interferons, chemokines and growth factors, were analysed with Bio-Plex Pro™ Human Cytokine 27-plex Assay (Bio-Rad Laboratories, Hercules, CA): tumour necrosis factor (TNF), interferon gamma (IFNγ), interleukin 1 receptor antagonist (IL-1ra), IL-6, IL-8, IL-10, interferon-inducible protein 10 (IP-10), eotaxin, macrophage inflammatory protein 1 beta (MIP-1β), regulated on activation normal *T*-cell expressed and secreted (RANTES), basic fibroblast growth factor (BFGF) and platelet derived growth factor-BB (PDGF-BB).

Endothelium and platelet markers

Plasma levels of endothelial and platelet biomarkers; intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), syndecan-1, vascular endothelial (VE) cadherin, p-selectin and von Willebrand factor (vWF), were measured by enzyme immunoassays in duplicate using commercially available antibodies (R&D Systems and Agilent, Minneapolis, MN) in a 384 format using a combination of a CyBi-SELMA pipetting robot (Analytik Jena, Germany) and an automatic washer-dispenser (BioTek, Winooski, VN). Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (BioTek). Intra- and inter-assay coefficients of variation were <10% for all enzyme immunoassays.

Measurements under lower limit of detection were set to 0.01.

Post-cardiac arrest care and cardiovascular support

Comatose patients were cooled (36 °C) for 24 h according to the hospital's standard procedure. Percutaneous coronary intervention was performed if indicated.

In the presence of hypotension and clinical signs of tissue hypoperfusion, the circulation was optimized through fluid and vasopressor administration, based on the department's guidelines on circulatory support. A detailed description of the post-cardiac arrest care in this study has been published.[16]

Statistics

To describe the circulatory effects and the risk of mortality mediated by the inflammatory response after OHCA, we divided the analysis into three steps. Firstly, the associations between Utstein variables and biomarkers were assessed applying linear regression models. Secondly, the associations between biomarker concentrations and circulatory variables (norepinephrine dose, fluid infusion, cardiac output (CO), systemic vascular resistance (SVR), and mean arterial blood pressure (MAP)) at admission and day two were assessed in linear regression models. In both analyses, the associations were assessed at day zero (i.e. admission) and on day two (after ~35–40 h) in order to capture both the immediate and a delayed inflammatory response and circulatory effects after cardiac arrest. Finally, we used logistic regression of biomarkers at admission to estimate the odds ratio for 30-day mortality.

All biomarkers were binary logarithmic ($\log_2$) transformed to obtain normal distributions. Only biomarkers consistently associated with circulatory variables (over two measurements with $p < 0.1$) in the daily univariable analysis were included in the backward selection of variables in the multivariable regression models. We used the coefficient of determination (R^2) to assess the models' explanatory capabilities. In the case of heteroscedasticity, a regression model with robust standard error was used, and strongly collinear predictors were omitted from the analysis.

To describe the biomarker alteration over time, we stratified the study population into three groups, based on whether they were dead ("status 1"), still in ICU ("status 2") or transferred to ward in stable condition ("status 3") by day five. First, we showed stratified graphs of biomarker concentrations over all days. Then, we used one-way ANOVA and Tukey's method to determine if biomarker concentrations between groups were significantly different at day zero and day two.[23]

Data were extracted with the software Matlab (Mathworks Inc., Natick, MA), and the statistical analyses were performed with Stata 16.1 (StataCorp LCC, Collage Station, TX).

Sample size

This is a descriptive study, so no formal sample size calculation was performed.[24]

Ethics

The Regional Committee for Medical and Health Research Ethics, Central Norway Health Region (REK Midt, No. 2015/1807) approved the study. Participants or their proxies provided written consent.

Results

Study population

Among 65 consecutive patients assessed for eligibility, 15 patients were excluded (seven patients due to immediate withdrawal of life-support, two had septic aetiology, two patients not in need of ICU admission, three patients received VAD or ECMO and one patient underwent immediate surgery), and 50 patients included in the study.[17] Forty-two patients were comatose at admission, 44 received bystander cardiopulmonary resuscitation and 37 had ventricular fibrillation as initial rhythm (Table 1). The median response time was 9.5 min (first to third quartile (Q1–Q3) 5–13.5). ROSC was achieved after a median of 24 min (Q1–Q3: 14–32) from the time of the emergency call. By the end of day five, 12 patients were dead (status 1),

Table 1 – Demography for all patients and subgroups.

Characteristics of patients [1]	All N = 50 (100%)	Status 1 n = 12 (24%)	Status 2 n = 22 (44%)	Status 3 n = 16 (32%)
Age, years, mean (sd)	63 (15)	63 (19)	65 (13)	59 (16)
Male sex, no (%)	40 (80)	6 (50)	21 (95)	13 (81)
Body mass index, mean (sd)	28 (6.6)	29 (12)	28 (4.3)	26 (3.5)
Charlson comorbidity index, median (Q1–Q3)	3 (2–4)	3 (1.5–5)	4 (3–4)	2 (1.5–4)
Witnessed cardiac arrest, no. (%)	42 (84)	8 (66)	19 (86)	15 (93)
Bystander CPR, no (%)	44 (88)	11 (91)	19 (86)	14 (87)
Time to ACLS, min, median (Q1–Q3)	9.5 (5–14)	14 (7–23)	10 (5–13)	6 (4–10)
Shockable initial rhythm, no. (%)	39 (78)	3 (25)	22 (100)	14 (87)
Number of defibrillations, median (Q1–Q3)	2 (1–4)	0 (0–2)	3 (1–7)	2 (1–2.5)
Time to ROSC, min., median (Q1–Q3)	24 (14–32)	27.5 (20–37)	25.5 (18–36)	14 (8–28)
Presumed cardiac etiology, no. (%)	42 (84)	6 (50)	21 (95)	15 (93)
Circulatory shock in ER [2], no. (%)	18 (36)	7 (58)	9 (40)	2 (12)
Comatose at admission [3], no. (%)	42 (84)	12 (100)	22 (100)	8 (50)
Certain pulmonary aspiration, no. (%)	9 (18)	5 (41)	2 (9)	2 (12)
Initial pH, mean (sd)	7.18 (0.14)	7.0 (0.13)	7.19 (0.14)	7.27 (0.09)
Initial base excess, mmol/L, mean (sd)	−9.4 (7.4)	−16.2 (4.9)	−9.29 (5.4)	−7.1 (4.7)
Initial lactate level, mmol/L, mean (sd)	6.7 (4.2)	11.4 (3.3)	5.5 (3.5)	4.8 (3.2)
Simplified Acute Physiology Score II, mean (sd)	62 (19)	72 (14)	68 (11)	44 (18)
30-days mortality	16 (32)	12 (100)	3 (13)	1 (6)

ACLS: advanced cardiovascular life support; CPR: cardiopulmonary resuscitation; ER: emergency room; ROSC: return of spontaneous circulation; sd: standard deviation; Q1–Q3: first to third quartile.

[1] The study population was divided into three groups, based on whether they were dead ("status 1"), still in ICU ("status 2") or transferred to ward ("status 3") by day five.

[2] Systolic blood pressure < 90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure > 90 mmHg.

[3] Comatose were patients that were intubated and gave no contact (GCS < 8). Awake patients were responsive and followed instructions.

22 were still in the ICU (status 2) and 16 were transferred to ward in stable circulatory condition (status 3). Three patients from status 2, and one from status 3, died within 30 days. Demographic results are given in Table 1. Mean length of day zero was 11 h (standard deviation; 5 h).

During the ICU stay, the median mCPIS score peaked on day four, when 12 of 27 patients had a score ≥6, and 26 of 27 patients received antibiotics (Supplementary Table 1).

Plasma biomarkers

The plasma concentration of the complement activation products TCC and C3bc, the cytokines IL-1ra, IL-8 and RANTES, and the endothelial cell markers syndecan-1 and VE-cadherin were highest at admission and thereafter gradually decreased (Fig. 1 and Supplementary Fig. 1), whereas IL-6 remained elevated during the study (Fig. 1). CRP increased from admission until day two (Fig. 1), whereas vWF showed a more mixed pattern (Supplementary Fig. 1). With exception of VE-cadherin and RANTES, patients in status 1 (dead by day 5) had the highest concentrations of all biomarkers, and status 3 patients (transferred to ward by day 5) had the lowest (Fig. 1 and Supplementary Table 2).

TNF, IFNγ, IL-10, IP-10, eotaxin, MIP-1β, BFGF, PDGF-BB, ICAM-1, VCAM-1 and P-selectin were elevated but not consistently associated with outcome, and thus omitted from further analyses (Supplementary Fig. 2 and Supplementary Tables 3 and 4).

The number of blood samples per day is shown in Supplementary Table 5.

Association between cardiac arrest and inflammation

The association between Utstein variables and biomarker concentrations are shown in Table 2. In the multivariable linear regression analyses, time to ROSC and high lactate concentrations at admis-

Fig. 1 – Biomarker alterations during study period. Log_2 transformed concentrations. The study population was divided into three groups, based on whether they were dead, still in ICU or transferred to ward by day five. A. Terminal complement complex (TCC), significant difference in concentration at admission between "dead" and "transferred to ward", B. Activated complement 3b (C3bc), significant difference in concentration at admission between "dead" and "transferred to ward" C. Interleukin 1 receptor antagonist (IL-1-ra), significant difference in concentration at day two between "transferred to ward" and both "still in ICU" and "dead", D. Interleukin 6 (IL-6), significant difference in concentration at admission between "dead" and both "transferred to ward" and "still in ICU", significant difference in concentration at day two between "transferred to ward" and "still in ICU", E. Interleukin 8 (IL-8), significant difference in concentration at admission between "dead" and both "still in ICU" and "transferred to ward", significant difference in concentration at day two between "transferred to ward" and "still in ICU" F. C-reactive protein (CRP), significant difference in concentration at day two between "transferred to ward" and both "dead" and "still in ICU" G. Syndecan-1. H. Vascular endothelial (VE) cadherin, significant difference in concentration at admission between "dead" and "transferred to ward".

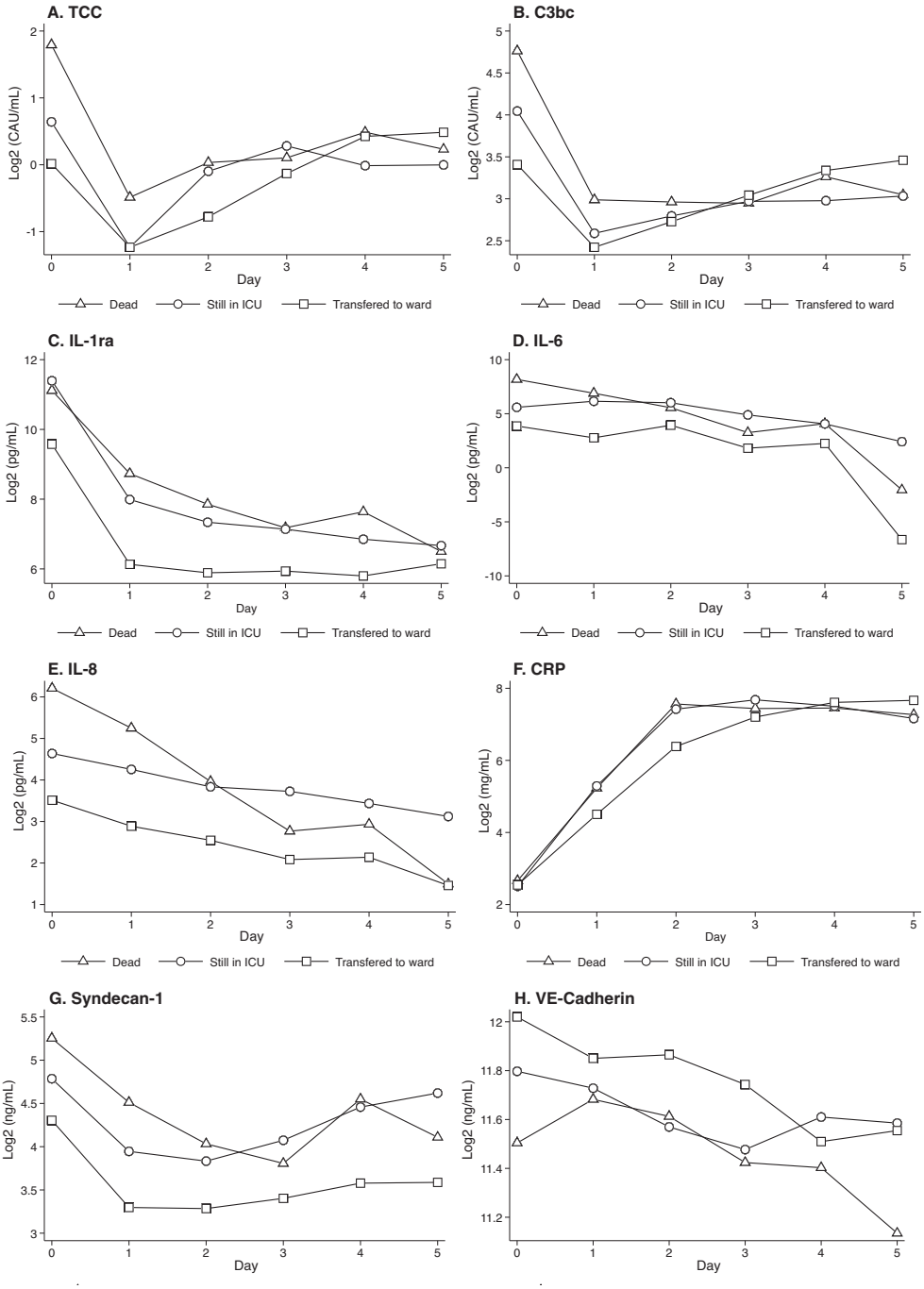
A. TCC
Log2 (CAU/mL)
B. C3bc
Log2 (CAU/mL)
C. IL-1ra
Log2 (pg/mL)
D. IL-6
Log2 (pg/mL)
E. IL-8
Log2 (pg/mL)
F. CRP
Log2 (mg/mL)
G. Syndecan-1
Log2 (ng/mL)
H. VE-Cadherin
Log2 (ng/mL)
Day
Dead
Still in ICU
Transfered to ward

Table 2 – Association between biomarkers at admission (day 0) and Utstein cardiac arrest variables.

	TCC	C3bc	IL-1ra	IL-6	IL-8
Age, 5 years					
Univariable	0.95 (0.84–1.06)	0.99 (0.91–1.08)	1.04 (0.88–1.21)	1.00 (0.82–1.22)	0.98 (0.88–1.10)
Multivariable	–	–	–	–	–
Comorbidity score [1]					
Univariable	0.91 (0.78–1.06)	0.98 (0.87–1.09)	0.90 (0.73–1.10)	0.83 (0.65–1.07)	0.88 (0.76–1.02)
Multivariable	–	–	–	–	–
Shockable rhythm					
Univariable	0.53 (0.23–1.23)	0.54 (0.29–1.01)	1.31 (0.41–4.14)	0.17 (0.04–0.68)	0.30 (0.14–0.66)
Multivariable	–	–	–	–	–
Time to ROSC, 5 min					
Univariable	1.20 (1.08–1.33)	1.17 (1.08–1.26)	1.22 (1.05–1.41)	1.41 (1.18–1.68)	1.24 (1.13–1.37)
Multivariable	1.13 (1.01–1.26)	1.14 (1.05–1.23)	1.21 (1.05–1.40)	1.18 (1.03–1.35)	1.17 (1.08–1.27)
Lactate in ER, mmol/L					
Univariable	1.13 (1.05–1.22)	1.08 (1.02–1.14)	1.08 (0.97–1.20)	1.28 (1.16–1.41)	1.18 (1.10–1.26)
Multivariable	1.10 (1.02–1.19)	1.05 (0.99–1.11)	–	1.21 (1.10–1.33)	1.12 (1.04–1.20)
Pulmonary aspiration					
Univariable	1.92 (0.77–4.75)	1.66 (0.85–3.24)	3.15 (0.95–10.4)	6.15 (1.36–27.8)	3.37 (1.44–7.91)
Multivariable	–	–	2.83 (0.92–8.70)	3.57 (1.35–9.41)	2.71 (1.05–6.99)
R^2 Multivariable model	0.25 adjusted	0.27 adjusted	0.16 adjusted	0.47 adjusted	0.53 robust
	RANTES	**CRP**	**Syndecan-1**	**VE-cadherin**	**vWF**
Age, 5 years					
Univariable	0.95 (0.92–0.99)	0.99 (0.95–1.03)	0.98 (0.90–1.07)	0.98 (0.95–1.01)	0.98 (0.92–1.05)
Multivariable	–	–	–	–	
Comorbidity score [1]					
Univariable	0.95 (0.90–0.99)	0.98 (0.93–1.04)	0.92 (0.82–1.02)	1.00 (0.96–1.04)	0.94 (0.86–1.02)
Multivariable	–	–	–	–	–
Shockable rhythm					
Univariable	1.15 (0.85–1.55)	0.83 (0.60–1.16)	0.57 (0.30–1.06)	1.34 (1.08–1.66)	0.79 (0.49–1.27)
Multivariable	–	–	–	1.35 (1.09–1.67)	–
Time to ROSC, 5 min					
Univariable	1.02 (0.98–1.07)	1.01 (0.97–1.06)	1.16 (1.07–1.25)	0.96 (0.93–0.99)	1.07 (1.01–1.14)
Multivariable	–	–	1.12 (1.03–1.21)	0.97 (0.94–0.99)	–
Lactate in ER, mmol/L					
Univariable	1.00 (0.97–1.03)	1.00 (0.97–1.04)	1.11 (1.05–1.18)	0.97 (0.95–1.00)	1.03 (0.98–1.08)
Multivariable	–	–	1.08 (1.02–1.15)	–	–
Pulmonary aspiration					
Univariable	0.84 (0.61–1.16)	1.76 (1.28–2.41)	1.23 (0.61–2.46)	0.96 (0.75–1.24)	0.80 (0.48–1.35)
Multivariable	–	–	–	–	–
R^2 Multivariable model	–	–	0.32 adjusted	0.23 adjusted	–

C3bc: activated complement 3b; CRP: C-reactive protein; ER: emergency room; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secreted; ROSC: return of spontaneous circulation; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

[1] Charlson Comorbidity Index.

sion were significantly associated with higher levels of TCC, C3bc, IL-1ra, IL-6, IL-8 and syndecan-1 at admission, and lower levels of VE-cadherin at admission (Table 2). In general, the clinical variables in the model predicted a substantial part of biomarker variability.

On day 2, only TCC and syndecan-1 were associated with the Utstein variables in the multivariable analysis (Supplementary Table 6).

Association between inflammation and circulation

Linear regression analysis of the associations between biomarker concentrations and circulatory variables and organ failure (SOFA score) at admission and at day two are shown in Table 3 and Table 4, respectively. A consistent finding was that higher levels of C3bc, IL-6, IL-8 and syndecan-1, and lower level of VE-cadherin, was associated with lower MAP, CO and SVR, and higher noradrenaline dosages, higher SOFA scores, and increased fluid support. The model indicates that a substantial part of circulatory variability can be explained by the biomarker concentrations.

Association between inflammation and mortality

In multivariable logistic regression analyses of admission biomarkers, the odds ratio for mortality within 30 days of admission was 1.86 and 2.01 for each two-fold increase in plasma concentration of TCC and IL-6, respectively (Table 5). Biomarker concentrations for survivors and non-survivors are shown in Supplementary Table 7.

Discussion

In this study, we found a marked and broad inflammatory response in patients after cardiac arrest, which was substantially associated with clinical outcome. Longer time to ROSC and higher lactate at admis-

Table 3 – Association between two-fold increase in biomarker concentrations and outcome at admission (day 0).

Biomarker	**MAP**, mmHg		**CO**, L/min		**SVR**, dynes/*sec*/cm^5	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	−0.8 (−2.6 to 1.0)	–	−0.2 (−0.4 to 0.0)	−0.5 (−0.9 to −0.1)	25 (−81 to 131)	135 (5–266)
C3bc	−1.2 (−3.7 to 1.2)	–	−0.1 (−0.4 to 0.2)	0.5 (−0.1 to 1.1)	5 (−134 to 144)	–
IL-1ra	−1.1 (−2.4 to 0.3)	–	0.0 (−0.2 to 0.1)	–	17 (−56 to 91)	–
IL-6	−0.9 (−1.9 to 0.1)	–	0.0(−0.2 to 0.1)	–	12 (−65 to 90)	–
IL-8	−1.7 (−3.5 to 0.0)	–	−0.1 (−0.3 to 0.2)	–	9 (−91 to 109)	–
RANTES	5.9 (1.2–10)	6.9 (2.3–11)	0.2 (−0.7 to 1.2)	–	–233 (−642 to 175)	–
CRP	0.1 (−4.5 to 4.7)	–	0.1 (−0.5 to 0.6)	–	−67 (–322 to 188)	–
Syndecan-1	−2.6 (−4.9 to −0.3)	−3.0 (−5.2 to −0.9)	0.0 (−0.3 to 0.3)	–	−96 (–232 to 40)	−216 (−389 to −43)
VE-Cadherin	6.2 (−0.2 to 12)	–	0.6 (−0.3 to 1.5)	–	−203 (−620 to 213)	–
vWF	1.9 (−1.1 to 5.1)	–	−0.1 (−0.5 to 0.4)	–	−7 (−207 to 193)	–
R^2		0.22 adjusted		0.12 adjusted		0.15 adjusted
Biomarker	**Norepinephrine**, μg/kg/min		**Fluids**, mL/hr		**SOFA**, points	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	0.01 (0.00–0.03)	−0.04 (−0.07 to -0.01)	120 (70–178)	95 (0–190)	0.4 (−0.1 to 1.0)	−1.1 (−2.0 to −0.1)
C3bc	0.03 (0.01–0.04)	0.05 (0.01–0.08)	144 (62–225)	–	0.9 (0.2–1.6)	1.8 (0.3–3.2)
IL-1ra	0.01 (−0.01 to 0.02)	–	−1 (−52 to 49)	−54 (−113 to 4)	0.5 (0.1–0.9)	–
IL-6	0.01 (0.01–0.02)	0.01 (0.01–0.02)	44 (6–81)	–	0.4 (0.1–0.7)	0.4 (0.1–0.7)
IL-8	0.03 (0.01–0.04)	–	98 (36–160)	81 (9–153)	0.7 (0.2–1.3)	–
RANTES	0.01 (−0.03 to 0.06)	0.03 (0.00–0.07)	176 (−13 to 364)	–	−1.2 (−2.8 to 0.4)	–
CRP	−0.02 (−0.06 to 0.02)	–	−16 (−192 to 160)	–	0.7 (−0.7 to 2.2)	–
Syndecan-1	0.02 (0.00–0.07)	–	96 (10–181)	–	0.6 (−0.1 to 1.4)	–
VE-Cadherin	−0.05 (−0.10 to 0.00)	−0.04 (−0.1 to 0.01)	−312(−548 to −77)	–	−3.1 (−5.1 to −1.1)	–
vWF	0.01 (−0.01 to 0.04)	–	107 (−9 to 222)	–	0.4 (−0.6 to 1.4)	–
R^2		0.31 adjusted		0.36 robust		0.23 robust

C3bc: activated complement 3b; CO: cardiac output; CRP: c-reactive protein; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secreted; MAP: mean arterial pressure; SOFA: Sequential Organ Failure Assessment; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

sion was significantly associated with complement activation, cytokine release and endothelial glycocalyx injury. Which in turn were significantly associated with compromised circulation and increased need of circulatory support in the ICU. Finally, TCC and IL-6 at admission were significantly associated with 30-days mortality.

The inflammation after OHCA has previously been compared with sepsis, due to the similarity with the biochemical pattern and the typical circulatory failure; i.e. vasodilatation and capillary leakage.[25] The circulatory failure in sepsis is suggested to be caused by dysfunction of the endothelial barrier, where the endothelial glycocalyx is a central component.[26–28] Inflammation *per se*, and therapeutic volume expansion, may cause shedding of endothelial glycocalyx, leading to capillary leakage and exposure of pro-inflammatory and pro-coagulant proteins that amplifies the immune response.[29,30]

In our study, time to ROSC and initial lactate level were associated with complement activation (TCC and C3bc), pro-inflammatory cytokines (IL-6 and IL-8) and markers of glycocalyx shedding (syndecan-1). The association between these biomarkers and circulatory variables had a time-dependent pattern: Complement activation was initially associated with lower MAP, CO and SVR, and increased need of circulatory support, while pro-inflammatory cytokines showed a consistent association, and endothelial biomarkers a delayed association with the same circulatory patterns. This is in line with previous findings that IL-6 was consistently associated with vasopressor support, while thrombomodulin and syndecan-1 showed a delayed pattern.[12]

Unexpected, VE-cadherin, a marker for endothelial injury, was found in higher concentrations in patients in status 3, but was also associated with improved levels of circulatory variables and lower SOFA score. We have no explanation for this counterintuitive relationship.

However, the different biomarkers role in a clinical setting should be interpreted cautiously. Firstly, the effect of inflammatory biomarkers cannot be consistently classified as either pro- or anti-inflammatory.[31] Secondly, the effect of an individual biomarker is time- and context-dependent, and different biomarkers also work in concert as part of complex networks and cascades.[32] Finally, as therapies are given to maintain organ function and life, the untreated effects are not observed in any ethically acceptable human studies. This might result in some illogical relationships. For instance, if a biomarker is associated with low MAP and CO, and a vasopressor is given to normalize MAP, the association with MAP will be masked, and a spurious association with a *calculated* high SVR occur.

Seventy per cent of the ICU patients received antibiotics at day two, suggesting a suspected bacterial infection. At the same time, 27% had a mCPIS score above five, indicative of pneumonia. Aspiration of gastric content is common during OHCA and can cause a sterile inflammation, which subsequently may develop into a bacterial pneumonia. Thus, it is conceivable that the inflammatory

Table 4 – Association between two-fold increase in biomarker concentrations and outcome at day 2.

Biomarker	**MAP**, mmHg		**CO**, L/min		**SVR**, dynes/*sec*/cm^5	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	−2.8 (−7.5 to 2.0)	–	0.0 (−0.7 to 0.7)	0.8 (0.1 to 1.4)	0 (−179 to 69)	–
C3bc	−3.3 (−10.5 to 4.0)	–	0.3 (−0.7 to 1.2)	−0.8 (−1.6 to −0.1)	−89 (−250 to 72)	–
IL-1ra	−1.8 (−4.3 to 0.8)	–	0.1 (−0.2 to 0.5)	1.5 (0.8–2.1)	−25 (−84 to 34)	−146 (−257 to −35)
IL-6	−1.7 (−3.5 to 0.01)	−1.3 (−2.4 to −2.0)	0.0 (−0.2 to 0.3)	–	−30 (−74 to 13)	−79 (−136 to −22)
IL-8	−1.6 (−4.9 to 1.6)	–	−0.1 (−0.6 to 0.3)	−1.6 (−2.1 to −1.1)	−0.1 (−78 to 77)	273 (108–439)
RANTES	5.0 (−0.4 to 10)	–	0.0 (−0.9 to 1.0)	−0.5 (−1.0 to −0.02)	97 (−61 to 256)	–
CRP	−2.9 (−7.1 to 1.3)	–	−0.2 (−1.1 to 0.7)	–	−91 (−243 to 60)	–
Syndecan-1	−3.6 (−8.6 to 1.4)	–	−0.2 (−0.8 to 0.5)	−0.8 (−1.5 to −0.01)	−17 (−136 to 103)	–
VE-Cadherin	12 (3.4–21)	11 (0.2–21)	1.3 (0.1–2.5)	1.8 (0.7–2.9)	3.1 (−231 to 238)	–
vWF	−1.8 (−4.5 to 0.9)	–	−0.2 (−0.6 to 0.2)	–	–32 (−102 to 38)	–
R^2		0.24 robust		0.69 robust		0.35 adjusted
Biomarker	**Noradrenaline**, μg/kg/min		**Fluids**, mL/hr		**SOFA**, points	
2-fold increase	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
TCC	0.03 (0.00–0.06)	–	26 (3–49)	26 (3–49)	1.9 (0.3–3.6)	–
C3bc	0.00 (−0.04 to 0.05)	–	−13 (−49 to 24)	−43 (−75 to −10)	0.5 (−1.9 to 3.1)	–
IL-1ra	0.02 (0.01–0.04)	–	17 (6–29)	–	1.2 (0.4–2.1)	0.9 (0.3–1.6)
IL-6	0.02 (0.01–0.03)	0.01 (0.0–0.03)	12 (4–21)	–	0.9 (0.4–1.5)	–
IL-8	0.03 (0.01–0.05)	–	23 (8–37)	–	1.5 (0.4–2.5)	–
RANTES	−0.04 (−0.07–0.00)	–	−38 (−65 to −12)	−26 (−49 to −3)	−2.2 (−4.1 to −0.2)	–
CRP	0.04 (0.01–0.06)	–	34 (15–52)	–	2.9 (1.3–4.5)	–
Syndecan-1	0.05 (0.03–0.08)	0.04 (0.0–0.08)	34 (11–57)	28 (7–48)	2.2 (0.6–3.9)	–
VE-Cadherin	−0.06 (−0.12 to 0.00)	–	−50 (−96 to −4)	–	−4.7 (−7.9 to −1.6)	−3.6 (−6.1 to −1.0)
vWF	0.01 (0.00–0.03)	–	12 (−1 to 25)	–	1.3 (0.4–2.1)	1.0 (0.3–1.7)
R^2		0.44 robust		0.44 adjusted		0.49 adjusted

C3bc: activated complement 3b; CO: cardiac output; CRP: c-reactive protein; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secreted; MAP: mean arterial pressure; SOFA: Sequential Organ Failure Assessment; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

Table 5 – Association between biomarkers at admission and death within 30-days.

Biomarker concentrations	Univariable analysis	Multivariable analysis
	Odds ratio (95% CI)	Odds ratio (95% CI)
TCC, per 2-fold increase	1.87 (1.21–2.89)	1.86 (1.02–3.40)
C3bc, per 2-fold increase	2.23 (1.27–3.89)	–
IL-1ra, per 2-fold increase	1.23 (0.93–1.63)	–
IL-6, per 2-fold increase	1.67 (1.20–2.32)	2.01 (1.20–3.37)
IL-8, per 2-fold increase	2.35 (1.41–3.92)	–
RANTES, per 2-fold increase	0.67 (0.26–1.75)	–
CRP, per 2-fold increase	1.28 (0.56–2.93)	–
Syndecan-1, per 2-fold increase	1.43 (0.91–2.27)	0.39 (0.15–1.00)
VE-cadherin, per 2-fold increase	0.22 (0.05–0.90)	–
vWF, per 2-fold increase	1.38 (0.76–2.53)	–
		Pseudo R^2 = 0.24

C3bc: activated complement 3b; CI: confidence interval; CRP: c-reactive protein; IL: interleukin; RANTES: regulated on activation normal *T*-cell expressed and secrete; TCC: terminal complement complex; vWF: von Willebrand factor.

response we observed is a combination of ischemia and reperfusion injury, aspiration pneumonitis and infections. However, Oppert and co-workers found that the abrupt rise in acute phase proteins after cardiac arrest was similar in patients with and without infection.[33] Bro-Jeppesen and co-workers drew a similar conclusion regarding the elevated levels of pro-inflammatory cytokines after cardiac arrest.[6] Thus, to diagnose pneumonia after OHCA using biomarkers alone may be misleading.

Complement activation products (C3bc) reflect activation of all initial pathways, whereas terminal complement complex (TCC) reflects complete activation of the terminal pathway. TCC exists in two forms; a soluble form (sC5b-9) that we measured in plasma, and in a membrane form (the membrane attack complex). Low levels of complement regulatory protein MAp19, high levels of complement C3bc and TCC, together with IL-6 have previously been shown to be associated with mortality after OHCA.[7,9,34,35] Accordingly, we found

that for every 2-fold increase in TCC and IL-6 levels at admission, the odds ratio for death within 30 days nearly doubled.

Unfortunately, therapeutic hypothermia has not been shown to alter the inflammatory response,[6] and there are currently no specific treatment for PCAS. Additionally, anti-inflammatory medications have to date not improved the outcome in critical illness.[36] However, a recent study on reducing inflammation and myocardial injury after OHCA with the IL-6 receptor blocker tocilizumab, found promising effects on biomarker release, but was underpowered for detecting change in mortality.[37] Complement inhibition might also be an alternative therapeutic approach in the future.[38] The clinical application of therapeutic complement inhibitors, has recently been extensively reviewed and seems promising.[39]

Strength and limitations

The strength of our study is that all patients were treated at one centre adhering to one protocol, which renders the use of circulatory support comparable. Furthermore, blood samples were drawn for all patients immediately after ICU admission and thereafter daily and prepared and stored according to a strict protocol to reflect *in vivo* degree of complement activation and cytokine release.[22,40] Also, the circulation was monitored, for most patients, using a Swan-Ganz catheter that provides more detailed hemodynamic measurements than routinely obtained. We acknowledge several limitations. Firstly, the generalizability might be limited by the size and the single-centre study design. Secondly, our cohort reflects a mixture of aetiologies and thus reflects a normal ICU population, but this might also make interpretation of the results more difficult than for a homogenous aetiological cohort. Thirdly, the sickest patients were more prone to aspiration and pneumonia that might affect the observed differences in biomarker concentrations. Fourthly, we chose to use a two-fold increase in concentration as the multiplicator for all biomarkers. However, the magnitude of change for the different biomarkers that reflect a physiological response is likely variable.

Conclusion

Long time to ROSC and high lactate level at admission were associated with higher levels of pro-inflammatory biomarkers, including increased complement activation (TCC and C3bc), cytokines (IL-6, IL-8) and endothelial injury (syndecan-1), in plasma at admission. These biomarkers were associated with lower MAP, CO and SVR, and increased need of circulatory support. Patients that presented with high levels of TCC and IL-6 at admission had increased 30-days mortality. Thus, this study shows that a systemic inflammatory response, including complement activation, cytokine release and endothelial glycocalyx injury, is associated with cardiac arrest and circulatory failure.

CRediT authorship contribution statement

Halvor Langeland: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Project administration. **Jan Kristian Damås:** Formal analysis, Writing – original draft. **Tom Eirik Mollnes:** Formal analysis, Writing – original draft. **Judith Krey Ludviksen:** Formal analysis, Writing – review & editing. **Thor Ueland:** Formal analysis, Writing – review & editing. **Annika E. Michelsen:** Formal analysis, Writing – review & editing. **Magnus Løberg:** Methodology, Formal analysis, Writing – original draft. **Daniel Bergum:** Investigation, Writing – original draft. **Trond Nordseth:** Software, Data curation, Formal analysis, Writing – review & editing. **Nils Kristian Skjærvold:** Investigation, Writing – review & editing. **Pål Klepstad:** Conceptualization, Methodology, Investigation, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.11.026.

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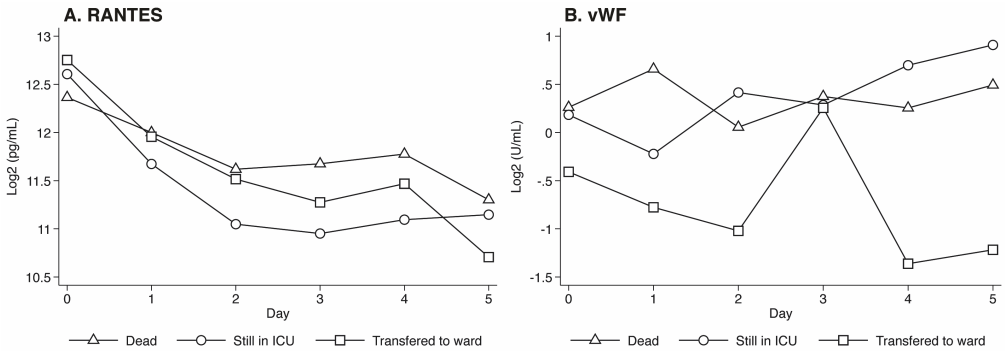
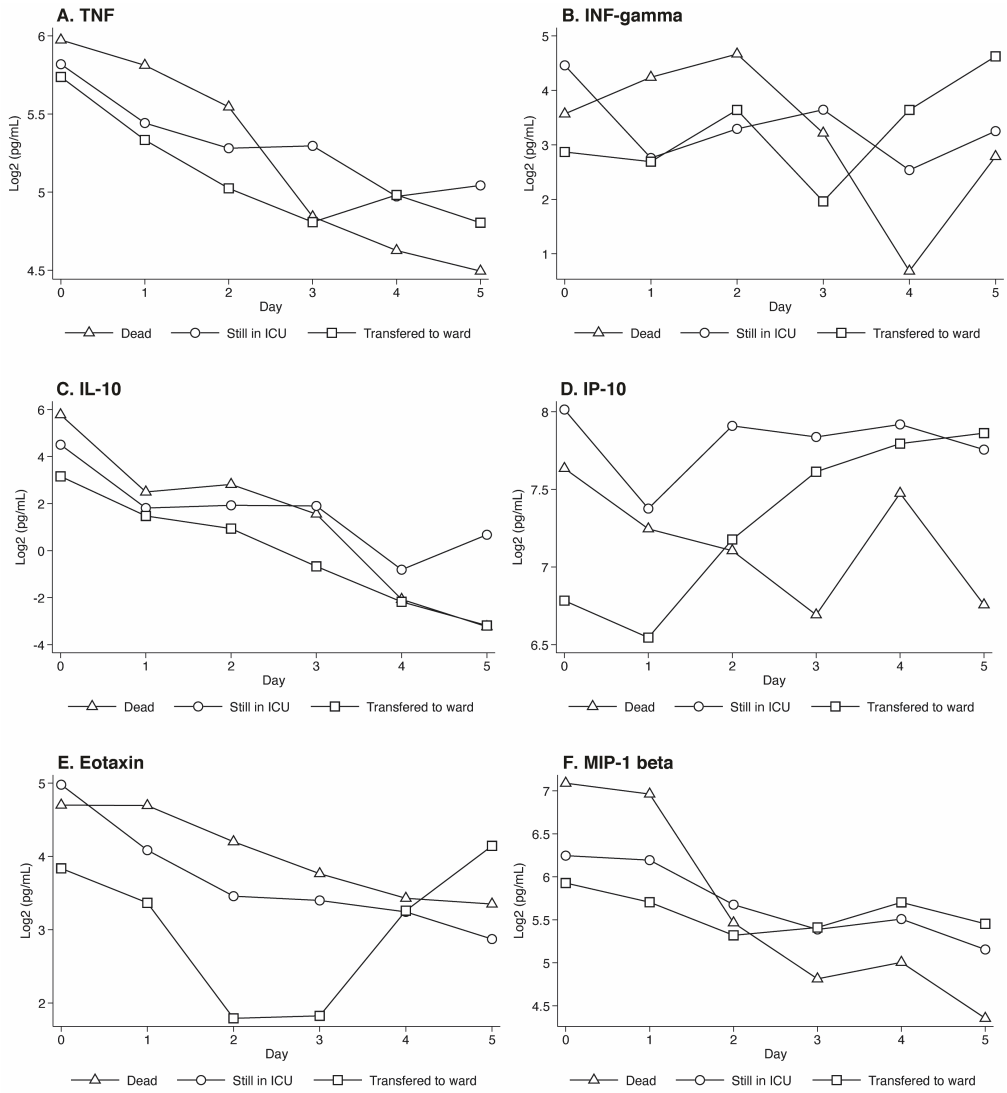
Supplementary Material

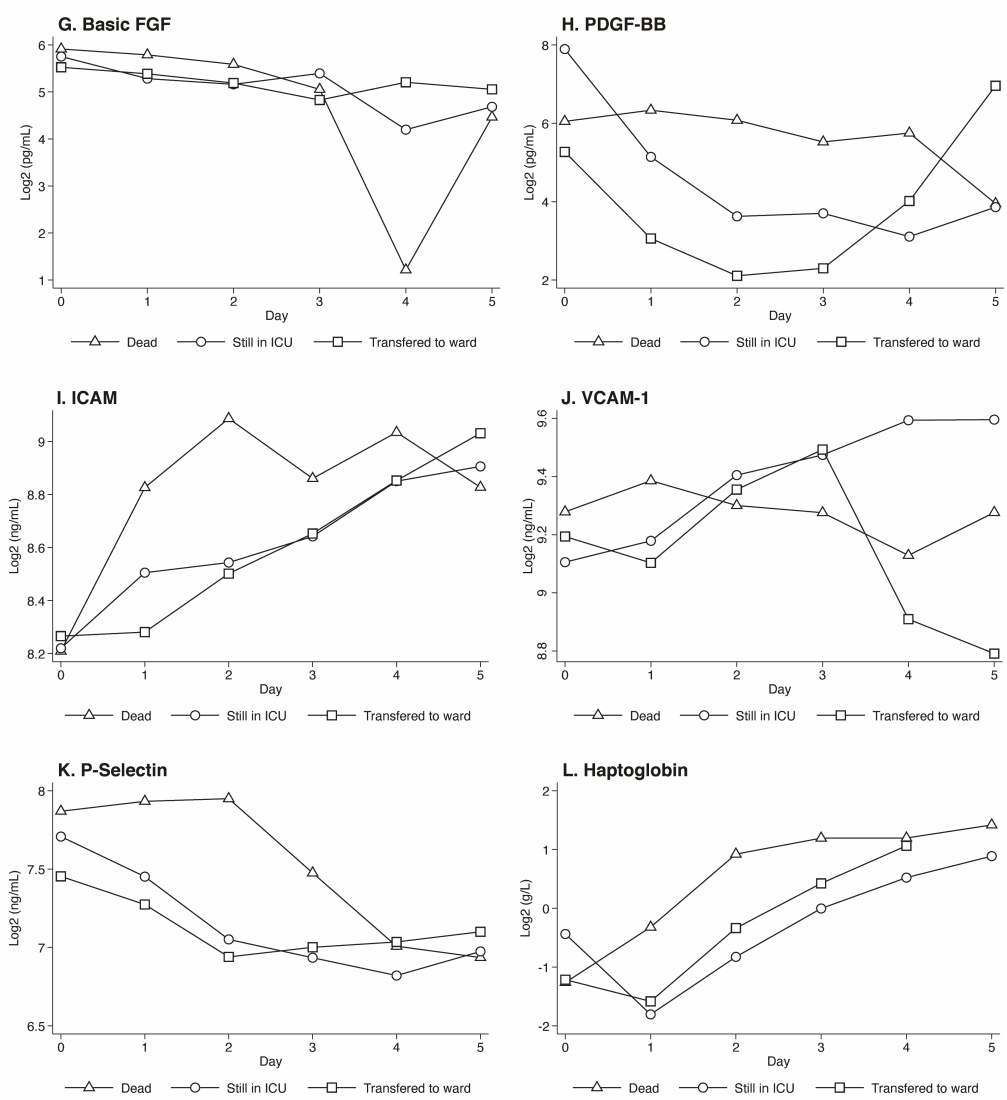
Langeland H, Damås JK, Mollnes TE, Ludviksen JK, Ueland T, Michelsen AE, Løberg M, Bergum D, Nordseth T, Skjærvold NK and Klepstad P. The inflammatory response is related to circulatory failure after out-of-hospital cardiac arrest: a prospective cohort study. Resuscitation. 2021;170:115-125



Supplementary figure 1. Biomarker alterations during study period.
Log2 transformed concentrations. The study population was divided into three groups, based on whether they were dead, still in ICU or transferred to ward by day five. **A.** Regulated on Activation Normal T-Cell Expressed and Secreted (RANTES). **B.** von Willebrand factor (vWF), significant difference in concentration at admission between "dead" and "transferred to ward".



Supplementary figure 2. Biomarker alterations during study period.
Log2 transformed concentrations. The study population was divided into three groups, based on whether they were dead, still in ICU or transferred to ward by day five. **A.** Tumor necrosis factor (TNF) **B.** Interferon gamma (IFNγ) **C.** Interleukin 10 (IL-10) **D.** interferon-inducible protein 10 (IP-10) **E.** Eotaxin, **F.** Macrophage inflammatory protein 1 beta (MIP-1β), **G.** Basic fibroblast growth factor (BFGF), **H.** Platelet derived growth factor-BB (PDGF-BB), **I.** Intercellular adhesion molecule 1 (ICAM-1). **J.** Vascular cell adhesion molecule 1 (VCAM-1). **K.** P-selectin, **L.** Haptoglobin.



Supplementary figure 2. (Continued)

Log2 transformed concentrations. The study population was divided into three groups, based on whether they were dead, still in ICU or transferred to ward by day five. **A.** Tumor necrosis factor (TNF) **B.** Interferon gamma (IFNγ) **C.** Interleukin 10 (IL-10) **D.** interferon-inducible protein 10 (IP-10) **E.** Eotaxin, **F.** Macrophage inflammatory protein 1 beta (MIP-1β), **G.** Basic fibroblast growth factor (BFGF), **H.** Platelet derived growth factor-BB (PDGF-BB), **I.** Intercellular adhesion molecule 1 (ICAM-1). **J.** Vascular cell adhesion molecule 1 (VCAM-1). **K.** P-selectin, **L.** Haptoglobin.

Supplementary Table 1: Modified Clinical Pneumonia Infection Score, CRP and antibiotics for all patients and subgroups [1].

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
All						
mCPIS, median (Q1–Q3)	5 (3-6)	3 (1-5)	4 (2-6)	5 (2-7)	5.5 (2.5-7)	5 (2.5-6)
mCPIS ≥ 6, no (%)	13 (26)	10 (22)	10 (27)	14 (38)	12 (44)	9 (36)
CRP, median (Q1–Q3)	5 (5-5)	32.5 (20-58)	157 (101-200)	184 (141-277)	180 (133-244)	142 (95-222)
Antibiotics, no (%)	0 (0)	16 (35)	26 (70)	28 (90)	26 (96)	25 (100)
	n=50	n=45	n=37	n=31	n=27	n=25
Status 1						
mCPIS, median (Q1–Q3)	5 (5-5.5)	5.5 (3-6)	6 (5-8)	7.5 (5.5 -9)	8 (6-10)	8 (8-8)
mCPIS ≥ 6, no (%)	3 (25)	4 (50)	3 (60)	3 (75)	3 (100)	2 (100)
CRP, median (Q1–Q3)	5 (5-5.5)	46 (21-137)	182 (182-278)	177 (165- 183)	180 (141-212)	212 (212-212)
Antibiotics, no (%)	0 (0)	2 (25)	4 (80)	3 (75)	3 (100)	2 (100)
	n=12	n=8	n=5	n=4	n=3	n=2
Status 2						
mCPIS, median (Q1–Q3)	5 (4-6)	4 (3-5)	4 (3-7)	5.5 (3-7)	5 (2-7)	5 (2-6)
mCPIS ≥ 6, no (%)	8 (36)	5 (23)	7 (32)	11 (50)	10 (45)	9 (41)
CRP, median (Q1–Q3)	5 (5-5)	37 (22-69)	180 (135-221)	223 (172-281)	180 (122-261)	142 (95-222)
Antibiotics, no (%)	0 (0)	12 (55)	20 (91)	22 (100)	22 (100)	22 (100)
	n=22	n=22	n=22	n=22	n=22	n=22
Status 3						
mCPIS, median (Q1–Q3)	2 (1-4)	1 (0-2)	1.5 (0-2)	1 (0-2)	1.5 (1-2)	1
mCPIS ≥ 6, no (%)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CRP, median (Q1–Q3)	5 (5-5)	24 (14-38)	103.5 (67-134)	117 (113-175)	226 (175-277)	277
Antibiotics, no (%)	0 (0)	2 (13)	2 (20)	3 (60)	1 (50)	1 (100)
	n=16	n=15	n=10	n=5	n=2	n=1

[1] The study population was divided into three groups, based on whether they were dead ("status 1"), still in ICU ("status 2") or transferred to ward ("status 3") by day five.
CRP: C-reactive protein; mCPIS: modified Clinical Pneumonia Infection Score; Q1–Q3: first to third quartiles.

Supplementary Table 2: One-way ANOVA and Tukey post hoc test of differences in biomarker concentrations between study groups at day 0 and day 2.

	ANOVA		Tukey, *p*-values		
Day 0	*F*	*p*	Status[1] 2 vs 1	Status 3 vs 1	Status 3 vs 2
TCC	3.82	0.03	0.15	0.02	0.50
C3bc	4.05	0.02	0.25	0.02	0.27
IL-1ra	3.09	0.05	0.93	0.19	0.05
IL-6	.8.87	0.00	0.03	0.00	0.13
IL-8	11.09	0.00	0.01	0.00	0.06
RANTES	1.37	0.26	0.52	0.23	0.75
CRP	0.20	0.82	0.81	0.89	0.98
Syndecan-1	1.77	0.18	0.59	0.15	0.51
VE-Cadherin	4.52	0.01	0.17	0.01	0.29
vWF	2.16	0.12	0.97	0.18	0.17
Day 2					
TCC	2.88	0.07	0.94	0.17	0.08
C3bc	0.28	0.75	0.88	0.73	0.94
IL-1ra	4.50	0.02	0.75	0.04	0.03
IL-6	3.49	0.04	0.89	0.33	0.03
IL-8	5.07	0.01	0.97	0.06	0.01
RANTES	2.37	0.10	0.23	0.96	0.19
CRP	6.34	0.00	0.93	0.03	0.01
Syndecan-1	2.25	0.12	0.86	0.19	0.16
VE-Cadherin	1.80	0.18	0.97	0.50	0.16
vWF	4.06	0.02	0.16	0.02	0.33

[1] Patient status by day 5: 1= dead, 2=still in ICU, 3=transferred to ward.
C3bc: activated complement 3b; CRP: C-reactive protein; IL: interleukin; RANTES: regulated on activation normal T-cell expressed and secreted; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor.

Supplementary Table 3: Univariable linear regression analysis of association between biomarker concentration at admission and Utstein cardiac arrest variables.

	TNF	INF-γ	IL-10	IP-10
Age, per 5 years	0.95 (0.91 - 1.00)	0.91 (0.77 - 1.08)	0.92 (0.81 - 1.03)	1.08 (0.98 - 1.19)
Charlson Comorbidity Index, points	1.00 (0.89 - 1.00)	0.96 (0.77 - 1.19)	0.79 (0.69 - 0.92)	1.16 (1.03 - 1.31)
Initial shockable rhythm, yes	0.92 (0.66 - 1.29)	1.68 (0.49 - 5.70)	0.36 (0.15 - 0.85)	1.18 (0.56 - 2.49)
Time to ROSC, per 5 min	1.04 (0.99 - 1.08)	1.06 (0.90 - 1.26)	1.24 (1.11 - 1.38)	1.03 (0.93 - 1.14)
Lactate at admission, per mmol/L	1.03 (0.99 - 1.06)	1.02 (0.90 - 1.16)	1.17 (1.08 - 1.26)	1.01 (0.95 - 1.07)
Certain pulmonary aspiration, yes	1.47 (1.04 - 2.07)	1.60 (0.43 - 6.02)	2.11 (0.81 - 5.48)	1.14 (0.51 - 2.56)

	Eotaxin	MIP-1b	Basic FGF	PDGF-BB
Age, per 5 years	0.98 (0.91 - 1.06)	1.00 (0.94 - 1.07)	0.96 (0.93 - 1.00)	0.90 (0.70 - 1.17)
Charlson Comorbidity Index, points	1.02 (0.92 - 1.13)	0.95 (0.87 - 1.03)	0.95 (0.91 - 1.00)	1.01 (0.72 - 1.41)
Initial shockable rhythm, yes	1.04 (0.58 - 1.87)	0.57 (0.36 - 0.92)	0.79 (0.61 - 1.04)	2.91 (0.44 - 19.28)
Time to ROSC, per 5 min	1.08 (1.01 - 1.17)	1.10 (1.03 - 1.17)	1.05 (1.01 - 1.08)	1.22 (0.95 - 1.58)
Lactate at admission, per mmol/L	1.02 (0.97 - 1.08)	1.07 (1.02 - 1.12)	1.03 (1.00 - 1.06)	0.98 (0.83 - 1.16)
Certain pulmonary aspiration, yes	0.94 (0.50 - 1.76)	1.21 (0.71 - 2.06)	1.17 (0.88 - 1.56)	1.81 (0.23 - 14.17)

	ICAM	VCAM-1	p-Selectin	Haptoglobin
Age, per 5 years	0.97 (0.95 - 1.00)	1.00 (0.97 - 1.04)	0.97 (0.93 - 1.01)	1.03 (0.89 - 1.19)
Charlson Comorbidity Index, points	0.98 (0.95 - 1.02)	1.04 (1.00 - 1.09)	0.95 (0.89 - 1.00)	1.02 (0.77 - 1.35)
Initial shockable rhythm, yes	1.08 (0.88 - 1.32)	0.85 (0.66 - 1.09)	0.99 (0.71 - 1.37)	1.50 (0.59 - 3.81)
Time to ROSC, per 5 min	1.00 (0.98 - 1.04)	1.00 (0.97 - 1.04)	1.05 (1.00 - 1.09)	1.00 (0.88 - 1.13)
Lactate at admission, per mmol/L	0.99 (0.97 - 1.01)	1.00 (0.98 - 1.03)	1.02 (0.99 - 1.06)	0.93 (0.86 - 1.02)
Certain pulmonary aspiration, yes	1.12 (0.91 - 1.39)	0.95 (0.72 - 1.24)	1.15 (0.81 - 1.63)	-

BFGF: basic fibroblast growth factor; ICAM-1: intercellular adhesion molecule 1; IFNγ: interferon gamma; IL-10: interleukin 10; IP-10: interferon-inducible protein 10; MIP-1β: macrophage inflammatory protein 1 beta; PDGF-BB: platelet derived growth factor-BB; ROSC: return of spontaneous; TNF: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule 1.

Supplementary Table 4. Univariable linear regression analysis of association between two-fold increase in biomarker concentrations and outcome at day 0 and 2.

Biomarker 2-fold increase	MAP, mmHg		CO, L/min		SVR, dynes/sec/cm^5	
	Day 0	Day 2	Day 0	Day 2	Day 0	Day 2
TNF	1.3 (-3.2-1.2)	3.3 (-4.0-10)	0.5 (-0.2-1.1)	0.6 (-0.4-1.5)	-224 (-521-72)	-27 (-193-138)
INF-γ	0.7 (-0.4- 1.9)	0.9 (-0.6-2.4)	0.1 (-0.1-0.3)	0.2 (0.0-0.3)	-26 (-98-45)	-13 (-44-18)
IL-10	-1.6 (-3.2--0.01)	-0.2 (-2.1-1.6)	0.01 (-0.2-0.2)	-0.2 (-0.4-0.0)	-10 (-109-89)	24 (-14-63)
IP-10	-1.7 (-4.2-0.8)	-1.1 (-4.3- 2.1)	0.3 (-0.0-0.6)	0.1 (-0.3-0.6)	-97 (-238-43)	-22 (-97-53)
Eotaxin	-1.0 (-3.8- 1.7)	-0.4 (-1.5- 0.7)	0.3 (-0.1-0.6)	0.1 (-0.0-0.3)	-108 (-265-49)	-24 (-49-0)
MIP-1b	0.9 (-2.2-4.1)	-4.8 (-9.7- 0.2)	0.1 (-0.4-0.5)	-0.2 (-1.0-0.6)	29 (-169-229)	27 (-108-163)
Basic FGF	0.3 (-0.6-1.2)	1.3 (-3.3-5.9)	-0.1 (-0.9-0.6)	0.2 (-0.3-0.8)	3 (-328-334)	-18 (-120-83)
PDGF-BB	0.3 (-0.6-1.2)	-0.04 (-0.9-0.8)	0.3 (0.1-0.5)	0.1 (-0.01-0.2)	-114 (-188--40)	-14 (-33-5)
ICAM	5.1 (-2.5-12)	1.4 (-4.9-7.8)	0.5 (-0.6-1.6)	0.4 (-0.4-1.2)	-335 (-798-128)	-41 (-185-102)
VCAM-1	0.8 (-5.7-7.3)	1.3 (-8.1- 10.7)	0.1 (-0.7-0.9)	0.7 (-0.6-2.1)	-110 (-470-249)	-61 (-303-180)
p-Selectin	-1.3 (-6.1-3.5)	2.8 (-3.8- 9.4)	-0.3 (-0.9- 0.4)	0.2 (-0.8-1.2)	50 (-233-324)	3 (-167-173)
Haptoglobin	-0.1 (-6.2- 6.1)	2.9 (-0.6-6.3)	-0.2 (-1.0-0.6)	0.4 (-0.2- 0.9)	106 (-100-313)	-2 (-101-97)

Biomarker 2-fold increase	Norepinephrine, µg/kg/min		Fluids, mL/hr		SOFA, points	
	Day 0	Day 2	Day 0	Day 2	Day 0	Day 2
TNF-α	0.02 (-0.01-0.06)	0.02 (-0.02-0.07)	129 (-40-299)	4 (-32-41)	0.4 (-1.1-1.9)	0.8 (-1.8-3.3)
INF-γ	0.00 (-0.00-0.01)	0.00 (-0.00-0.01)	20 (-26-67)	-5 (-12-2)	0.0 (-0.4-0.4)	-0.1 (-0.7-0.4)
IL-10	0.01 (0.00-0.03)	0.00 (-0.01-0.01)	92 (34-150)	7 (-2-15)	0.7 (0.2- 1.2)	0.2 (-0.4-0.9)
IP-10	0.01 (-0.00-0.03)	0.01 (-0.00-0.04)	16 (-61-93)	0 (-17-16)	1.1 (0.6-1.7)	0.7 (-0.5-1.8)
Eotaxin	0.02 (0.00-0.05)	0.00 (-0.00-0.01)	54 (-44-152)	-3 (-9-2)	1.3 (0.5- 2.0)	0.2 (-0.2-0.6)
MIP-1b	0.03 (0.00-0.05)	0.02 (-0.01-0.05)	202 (100-303)	28 (4-52)	0.7 (-0.3-1.6)	1.1 (-0.7-2.9)
Basic FGF	0.05 (0.00-0.09)	-0.02 (-0.05-0.01)	344 (152-535)	-4 (-27-19)	0.6 (-1.3-2.5)	-0.4 (-2.1-1.2)
PDGF-BB	0.00 (-0.00-0.01)	0.00 (-0.00-0.01)	15 (-14-45)	-5 (-9-0)	0.3 (0.1-0.6)	0.01 (-0.3-0.3)
ICAM	-0.02 (-0.08-0.04)	0.01 (-0.03-0.05)	-164 (-449-120)	22 (-9-53)	-0.5 (-3.0-1.9)	1.2 (-0.9-3.4)
VCAM-1	0.00 (-0.05-0.05)	0.02 (-0.04-0.08)	-24 (-256-207)	-1 (-49-46)	0.4 (-1.6-2.4)	1.0 (-2.4-4.4)
p-Selectin	0.00 (-0.03-0.04)	0.00 (-0.04-0.04)	4 (-172-182)	20 (-12-54)	0.7 (-0.8-2.2)	1.4 (-0.9-3.8)
Haptoglobin	0.01 (-0.02-0.06)	0.00 (-0.03-0.02)	-25 (-370-319)	5 (-11-23)	0.3 (-1.1-1.8)	-0.5 (-1.7-0.7)

BFGF: basic fibroblast growth factor; CO: cardiac output; ICAM-1: intercellular adhesion molecule 1; IFNγ: interferon gamma; IL-10: interleukin 10; IP-10: interferon-inducible protein 10; MAP: mean arterial pressure; MIP-1β: macrophage inflammatory protein 1 beta; PDGF-BB: platelet derived growth factor-BB; SOFA: sequential organ failure assessment; SVR: systemic vascular resistance; TNF: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule 1.

Supplementary Table 5: Number of blood samples per day.

Patient status [1]	Admission	Day 1	Day 2	Day 3	Day 4	Day 5
1	12	8	5	4	3	2
2	22	22	22	22	22	22
3	16	15	10	5	2	1
Total	50	45	37	31	27	25

[1] The study population was divided into three groups, based on whether they were dead ("status 1"), still in ICU ("status 2") or transferred to ward ("status 3") by day five.

Supplementary Table 6. Linear regression analysis of association between biomarkers and Utstein cardiac arrest variables at day two

	TCC	C3bc	IL-1ra	IL-6	IL-8
Age, 5 years					
Univariable	1.04 (0.96-1.12)	1.03 (0.97-1.08)	0.99 (0.85-1.16)	1.04 (0.84-1.29)	0.99 (0.88-1.12)
Multivariable	1,14 (1.01-1.28)	-	-	-	-
Comorbidity score [1]					
Univariable	0.99 (0.91-1.08)	1.03 (0.97-1.08)	0.92 (0.79-1.07)	0.97 (0.78-1.21)	0.95 (0.84-1.07)
Multivariable	0.92 (0.82-1.03)	-	-	-	-
Shockable rhythm					
Univariable	0.87 (0.46-1.65)	1.05 (0.68-1.60)	0.46 (0.14-1.45)	0.80 (0.15-4.21)	0.51 (0.20-1.26)
Multivariable	-	-	-	-	-
Time to ROSC, 5 min					
Univariable	1.03 (0.96-1.10)	0.98 (0.94-1.03)	1.20 (1.07-1.34)	1.10 (0.93-1.32)	1.12 (1.02-1.23)
Multivariable	-	-	-	-	-
Lactate in ER, mmol/L					
Univariable	1.02 (0.97-1.08)	1.02 (0.99-1.06)	1.11 (1.02-1.21)	0.98 (0.86-1.11)	1.04 (0.96-1.11)
Multivariable	-	-	-	-	-
Pulmonary aspiration					
Univariable	1.39 (0.82-2.35)	1.02 (0.72-1.46)	1.37 (0.51-3.72)	1.47 (0.36-5.94)	1.26 (0.58-2.76)
Multivariable	1.79 (1.01-3.15)	-	-	-	-
R^2 Multivariable model	0.1 adjusted	-	-	-	-

	RANTES	CRP	Syndecan-1	VE-cadherin	vWF
Age, 5 years					
Univariable	1.00 (0.94-1.07)	1.01 (0.92-1.10)	1.01 (0.94-1.09)	0.99 (0.95-1.03)	0.95 (0.82-1.09)
Multivariable	-	-	-	0.94 (0.89-0.99)	-
Comorbidity score [1]					
Univariable	1.03 (0.96-1.11)	0.95 (0.87-1.04)	0.99 (0.92-1.08)	1.02 (0.98-1.07)	0.96 (0.83-1.11)
Multivariable	-	-	1.07 (1.02-1.13)	1.07 (1.01-1.14)	-
Shockable rhythm					
Univariable	1.04 (0.60-1.78)	0.93 (0.46-1.86)	0.75(0.41-1.36)	1.31 (0.97-1.77)	0.53 (0.18-1.60)
Multivariable	-	-	-	-	-
Time to ROSC, 5 min					
Univariable	0.93 (0.88-0.98)	1.10 (1.03-1.17)	1.10 (1.04-1.17)	0.97 (0.94-1.00)	1.11 (0.99-1.24)
Multivariable	-	-	1.10 (1.02-1.17)	-	-
Lactate in ER, mmol/L					
Univariable	1.01 (0.97-1.06)	1.04 (0.99-1.10)	1.07 (1.02-1.11)	0.99 (0.97-1.02)	1.02 (0.94-1.12)
Multivariable	-	-	1.06 (1.01-1.12)	-	-
Pulmonary aspiration					
Univariable	1.06 (0.67-1.68)	1.43 (0.81-2.55)	1.31 (0.80-2.16)	1.03 (0.79-1.34)	1.66 (0.65-4.18)
Multivariable	-	-	-	-	-
R^2 Multivariable model	-	-	0.47 robust	0.12 adjusted	-

[1] Charlson Comorbidity Index

C3bc: activated complement 3b; CRP: C-reactive protein; ER: emergency room; IL: interleukin; RANTES: regulated on activation normal T-cell expressed and secreted; ROSC: return of spontaneous circulation; TCC: terminal complement complex; VE: vascular endothelial; vWF: von Willebrand factor

Supplementary table 7: Biomarker concentrations at admission

	30-days mortality	
	Survivors (n=34)	Non-survivors (n=16)
TCC, CAU/mL, median (Q1–Q3)	0.9 (0.4-2.7)	3.4 (2.1-6.7)
C3bc, CAU/mL, median (Q1–Q3)	13 (7-21)	26 (15-60)
IL-1ra, pg/mL, median (Q1–Q3)	1634 (458-4956)	3613 (1363-9765)
IL-6, pg/mL, median (Q1–Q3)	27 (10-81)	193 (52-916)
IL-8, pg/mL, median (Q1–Q3)	15 (8-25)	80 (21-174)
RANTES, pg/mL, median (Q1–Q3)	6391 (5677-7415)	6237 (4836-8998)
CRP, mg/mL, median (Q1–Q3)	5 (5-5)	5 (5-6)
Syndecan-1, ng/mL, median (Q1–Q3)	24 (11-47)	28 (17-90)
VE-cadherin, ng/mL, median (Q1–Q3)	3775 (3053-4765)	3013 (2489-3774)
vWF, U/mL, median (Q1–Q3)	0.8 (0.6-1.7)	1.5 (0.6-2.1)
TNF, pg/mL, median (Q1–Q3)	48 (41-62)	70 (51-100)
INF-γ, pg/mL, median (Q1–Q3)	18 (9-25)	30 (15-53)
IL-10, pg/mL, median (Q1–Q3)	14 (7-24)	60 (25-131)
IP-10, pg/mL, median (Q1–Q3)	203 (90-428)	198 (119-307)
Eotaxin, pg/mL, median (Q1–Q3)	27 (12-33)	38 (22-51)
MIP-1b, pg/mL, median (Q1–Q3)	63 (45-103)	116 (66-226)
Basic-FGF, pg/mL, median (Q1–Q3)	45 (40-55)	57 (46-81)
PDGF-BB, pg/mL, median (Q1–Q3)	115 (46-367)	193 (49-571)
ICAM, ng/mL, median (Q1–Q3)	295 (240-352)	293 (251-376)
VCAM-1, ng/mL, median (Q1–Q3)	530 (443-712)	563 (455-780)
p-Selectin, ng/mL, median (Q1–Q3)	189 (142-240)	228 (148-292)
Haptoglobin, g/L, median (Q1–Q3)	0.8 (0.4-1.1)	0.4 (0.3-0.7)

BFGF: basic fibroblast growth factor; C3bc: activated complement 3b; CRP: c-reactive protein; ICAM-1: intercellular adhesion molecule 1; IFNγ: interferon gamma; IL: interleukin; IP-10: interferon-inducible protein 10; MIP-1β: macrophage inflammatory protein 1 beta; PDGF-BB: platelet derived growth factor-BB; RANTES: regulated on activation normal T-cell expressed and secreted; TCC: terminal complement complex; TNF: tumor necrosis factor; VCAM-1: vascular cell adhesion molecule 1VE: vascular endothelial; vWF: von Willebrand factor.

Paper III

openheart

Characteristics of circulatory failure after out-of-hospital cardiac arrest: a prospective cohort study

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ABSTRACT

Background Circulatory failure after out-of-hospital cardiac arrest (OHCA) as part of the postcardiac arrest syndrome (PCAS) is believed to be caused by an initial myocardial depression that later subsides into a superimposed vasodilatation. However, the relative contribution of myocardial dysfunction and systemic inflammation has not been established. Our objective was to describe the macrocirculatory and microcirculatory failure in PCAS in more detail.

Methods We included 42 comatose patients after OHCA where circulatory variables were invasively monitored from admission until day 5. We measured the development in cardiac power output (CPO), stroke work (SW), aortic elastance, microcirculatory metabolism, inflammatory and cardiac biomarkers and need for vasoactive medications. We used survival analysis and Cox regression to assess time to norepinephrine discontinuation and negative fluid balance, stratified by inflammatory and cardiac biomarkers.

Results CPO, SW and oxygen delivery increased during the first 48 hours. Although the estimated afterload fell, the blood pressure was kept above 65 mmHg with a diminishing need for norepinephrine, indicating a gradually re-established macrocirculatory homoeostasis. Time to norepinephrine discontinuation was longer for patients with higher pro-brain natriuretic peptide concentration (HR 0.45, 95% CI 0.21 to 0.96), while inflammatory biomarkers and other cardiac biomarkers did not predict the duration of vasoactive pressure support. Markers of microcirculatory distress, such as lactate and venous-to-arterial carbon dioxide difference, were normalised within 24 hours.

Conclusion The circulatory failure was initially characterised by reduced CPO and SW, however, microcirculatory and macrocirculatory homoeostasis was restored within 48 hours. We found that biomarkers indicating acute heart failure, and not inflammation, predicted longer circulatory support with norepinephrine. Taken together, this indicates an early and resolving, rather than a late and emerging vasodilatation.

Trial registration NCT02648061.

Key messages

What is already known about this subject?

► The postcardiac arrest syndrome compromise brain injury; myocardial dysfunction; and systemic inflammation response. In addition, patient comorbidities and the pathological process that caused the cardiac arrest often complicate the clinical course. The circulatory failure is believed to be caused by an initial myocardial depression that later subsides into a superimposed vasodilatation. Still, the relative contribution of myocardial dysfunction and systemic inflammation has not been established.

What does this study add?

► This prospective cohort study provides insight into the macrocirculatory and microcirculatory failure after cardiac arrest, with focus on the development of vasopressor need, energy and oxygen delivery, vascular resistance, oxygen consumption, lactate level and veno-arterial pCO_2 gap. In addition, the study explored the relative contribution of inflammation and cardiac dysfunction on circulatory failure after cardiac arrest.

How might this impact on clinical practice?

► In the literature the inflammatory vasodilatation after cardiac arrest is described as a later occurring phenomena that prevents discontinuation of vasopressors. However, in this study the vasodilatation was clinically early and resolving. Furthermore, biomarkers indicating acute heart failure, and not inflammation, predicted longer circulatory support with norepinephrine. These findings might influence the understanding of the underlying pathophysiology and act as a reminder of careful interpretation of vascular resistance measurements.

INTRODUCTION

Circulatory failure is frequently observed after out-of-hospital cardiac arrest (OHCA) as part of the postcardiac arrest syndrome (PCAS).[1] The current understanding is that the circulatory failure in PCAS is mainly caused by myocardial depression followed by superimposed inflammatory vasodilatation.[2–5] However, the interpretation of previous studies is challenging for several reasons. First, few studies use advanced haemodynamic measurements.[6 7] Second, some studies report systemic vascular resistance

(SVR) without complete information about each component of this equation.[4] Third, there is commonly a lack of detailed information on vasoactive medications and fluids used to achieve the haemodynamic results.[8] Fourth, therapeutic hypothermia has cardiovascular effects, such as bradycardia and vasoconstriction.[9] Fifth, the heterogeneous nature of patients' circulatory failure complicates the picture and there is reason to believe that there exist several different 'circulatory phenotypes' in patients with PCAS.[10–12] Finally, the aetiology of circulatory failure is mixed, and the relative contribution of myocardial dysfunction and systemic inflammation after global ischemia and reperfusion is yet to be established.[13] Thus, a more detailed description of circulatory disturbances after OHCA is warranted.

The total energy delivery from the heart to the circulation is measured per beat by stroke work (SW) or per minute by cardiac power output (CPO). Either way, the energy is in the form of a pressurised volume, which, dependent on the resistance to ejection, is distributed predominantly as flow or pressure. This balance between the heart's contractility and its afterload is described as ventriculo-arterial coupling.[14] CPO is the product of mean arterial pressure (MAP) and cardiac output (CO) and have been reported to correlate more strongly with mortality in cardiogenic shock than the variables from which it is derived.[15–18] However, like all CO-derived quantities, both CPO and SVR depend on heart rate. In comparison, SW and aortic elastance (Ea) is not affected by heart rate and reflects better the heart's beat-to-beat contractile function and afterload,[19] especially in patients with possible hypothermia-induced bradycardia.

The aim of this study was to describe the circulatory failure in PCAS, with focus on the development of vasopressor need, energy and oxygen delivery, vascular resistance, oxygen consumption, lactate level and veno-arterial pCO_2 gap. In addition, the study explored the relative contribution of inflammation and cardiac dysfunction on circulatory failure in PCAS.

METHODS

Study design

This was a preplanned analysis of a previously published single-centre, prospective, observational cohort study of 50 patients admitted to hospital with return of spontaneous circulation (ROSC) after OHCA.[12 20] Patients were included between January 2016 and November 2017. Only patients who were comatose at arrival were included in the current analysis.

Setting and eligibility

St. Olav's University Hospital is a 938-bed tertiary hospital in Trondheim, Norway, serving a population of approximately 700 000. Comatose adults admitted to the intensive care unit (ICU) with ROSC after OHCA were included in this study. Exclusion criteria were age <18 years, pregnancy, assumed septic or anaphylactic aetiology of cardiac arrest, transferal from another hospitals, decision to limit life-sustaining therapy on arrival, acute cardiothoracic surgery, intervention with extracorporeal membranous oxygenation (ECMO) or a ventricular assist device (VAD) before arrival at the ICU.

Study procedure

We followed the patients from time of ICU admission and the following 5 days, or until the patient died, ECMO, VAD or acute cardiothoracic surgery was necessary, life-prolonging therapy was limited, or if the patient was transferred to a general ward or another hospital during the study period. Day 0 had variable length depending on the time of inclusion, whereas day 1 started the following morning at 06:00.

All patients without contraindications received a pulmonary artery catheter (PAC) (Swan-Ganz CCombo, Edwards Lifesciences, USA) for continuous central haemodynamic measurements. Bleeding diathesis and implanted pacemaker were the main contraindications. If technical difficulties were experienced during catheter placement, the procedure was aborted. We calibrated the SvO_2 sensor two times a day.

We retrieved systolic and MAP, fluid administration, peripheral oxygen saturation (SpO_2), temperature, lactate concentration, arterial and venous partial pressure of carbon dioxide (CO_2), haemoglobin concentration (Hgb), heart rate and norepinephrine dosage from the electronic critical care management system (Picis CareSuite, Optum, USA). We retrieved CO, mean pulmonary artery pressure, stroke volume (SV) and mixed venous saturation (SvO_2) from patients with a PAC. Continuous data were sampled in 1 min resolution, and presented in 1-hour intervals. We obtained time from emergency call to advanced cardiovascular life support (ACLS), ROSC and ICU admission, initial cardiac rhythm, number of defibrillations, aetiology, and whether the arrest were witnessed and cardiopulmonary resuscitation commenced, all according to the Utstein cardiac arrest template,[21] Charlson Comorbidity Index[22] and clinical information on assessment and treatment from the prehospital and hospital records. Echocardiography was performed in all patients within 24 hours after admission by experienced cardiologists.

Simplified Acute Physiology Score 2 were registered 24 hours after admission,[23] and survival was registered after 30 days.

Haemodynamic calculations

CPO is measured in Watt (W) and calculated by CO (L/min)×MAP (mmHg) divided by 451. The normal resting CPO is ~1 W where <0.54 W is indicative of haemodynamic compromise.[24 25] SW is measured in Joule (J) and calculated by CPO×60 divided by heart rate. Clinically, Ea can be approximated non-invasively by systolic blood pressure (mmHg)×0.9 divided by SV (mL), with a normal range 1.4–3 mmHg/mL.[26 27] Oxygen delivery (DO_2) and consumption (VO_2) was calculated by 0.134×Hgb

(g/dL)×SpO_2 (%)×CO (L/min) and 0.134×Hgb (g/dL)×(SpO_2–SvO_2 (%))×CO (L/min), respectively.[28]

Blood samples

Interleukin (IL)-6, syndecan-1, pro-brain natriuretic peptide (BNP), troponin T and C reactive protein (CRP) concentrations were measured at inclusion and every morning during the study period. A detailed description of the blood sample handling is given in online supplemental text 1. Every 6 hours, we obtained an arterial blood gas sample, and two times a day a mixed venous blood gas sample, from which venous-to-arterial carbon dioxide difference ($P(v–a)CO_2$, kPa) was calculated.

Postcardiac arrest care and cardiovascular support

The patients were cooled to 36°C for 24 hours, with avoidance of hyperthermia (>37.5°C) for an additional 48 hours afterwards. Patients with suspected myocardial ischaemic aetiology of the cardiac arrest received coronary angiography and percutaneous revascularisation.

In the presence of hypotension (<65 mmHg) and clinical signs of tissue hypo-perfusion (such as cold clammy skin, prolonged capillary refill time, reduced urine output, increasing lactate and/or decreasing base excess), the circulation was optimised by fluid and vasopressor administration, based on the department's guidelines on circulatory support. A detailed description of the postcardiac arrest care in this study has been published previously.[20]

Statistical analysis

PCAS has been described as a 'sepsis-like syndrome',[2] and we hypothesise a prolonged vasopressor need, associated with high inflammatory biomarker concentrations, and a lack of macrocirculatory and microcirculatory coherence.

The mean circulatory development over time was graphically presented, with origin set to time of emergency call, and smoothed with 3 hours moving average to better visualise the trend. The differences between mean level of CPO, SW, Ea, SV, MAP and norepinephrine dosage at four and 48 hours after ICU admission were tested by Welch's unequal variance t-test.

We used survival analysis to explore the time to discontinuation of norepinephrine and daily negative fluid balance as a marker of circulatory stabilisation. Dobutamine was sporadic used in four patients and therefore not analysed. As the main aetiologies of circulatory shock in PCAS are inflammatory and/or cardiogenic, we compared high versus low levels of IL-6, syndecan-1, CRP, pro-BNP and troponin T, where time of emergency call served as origin for timing of biomarker measurement. Based on available blood samples, we stratified the population by the median of the area under the curve (AUC) for the biomarker measurements the first 52 hours after the emergency call.[29] Further, we used Cox regression to estimate the HR with 95% CI. Finally, we explored, with logistic regression, the demographic characteristics associated with the high biomarker group that significantly affected the duration of circulatory support.

Data were extracted with the software Matlab (Mathworks, USA), while the statistical analyses were performed with Stata V.16.0 (StataCorp). Obviously erroneous measurements (due to technical errors) were replaced by the mean value of the previous value and the value next minute.

Sample size

This was a descriptive study and no formal sample size calculation was performed.[30]

RESULTS

Study population and outcomes

Sixty-five consecutive patients (eight missing) were assessed for eligibility. Of these, eight patients were excluded due to not being comatose, seven patients due to immediate withdrawal of life-support, two had septic aetiology, two patients not in need of ICU admission, three patients received VAD or ECMO and one patient underwent immediate surgery. Thus, 42 patients were included in this analysis. The mean length of day 0 was 12 hours (SD 5 hours) from ICU admission. Demographic and circulatory data are presented in table 1, and corresponding test results for patients with high versus low biomarker levels are presented in online supplemental table 1.

Thirty-four of 42 patients received bystander cardiopulmonary resuscitation and 31 had shockable initial rhythm (table 1). From the time of the emergency call, the median time to ACLS was 10 min (first to third quartile (Q1–Q3) 5–15, min–max 0–36). ROSC was achieved after a median of 26 min (Q1–Q3 19–35, min–max 4–80), and median time to ICU admission was 133 min (Q1–Q3 102–168, min–max 26–263). Thirty patients (71 %) received a PAC. Within 30 days 15 of 42 patients had been declared dead.

Macrocirculation and circulatory support

Norepinephrine doses were gradually reduced, and after 48 hours, the mean dose of norepinephrine was halved, while the MAP had been maintained above 65 mmHg. Mean fluid balance was negative by day 4. Mean SV, SW and CPO increased from 50 mL, 0.5 J and 0.6 W on ICU admission to stable levels at approximately 80 mL, 0.8 J and 1 W, respectively, at 48 hours (figure 1A,B). Simultaneously, Ea was reduced approximately from 2.0 to 1.4 mmHg/mL (figure 1C). Additional macrocirculatory variables and more detailed echocardiographic results are presented in online supplemental figure 1 and table 2.

Kaplan-Meier estimates of the probability of on-going norepinephrine infusion and positive fluid balance are presented in figure 2 and online supplemental figure 2. The median time to discontinuation of norepinephrine was 75 hours for on-going norepinephrine infusion and the fourth morning for negative fluid balance. There was

Table 1 Demography for all patients

Characteristics of patients	All (n=42)
Age, years, mean (SD)	65 (15)
Male sex, no (%)	35 (83)
Body mass index, mean (SD)	28 (7)
Charlson Comorbidity Index, median (Q1–Q3)	3 (2–5)
Witnessed cardiac arrest, no. (%)	34 (81)
Bystander CPR, no (%)	37 (90)
Time to ACLS, min, median (Q1–Q3)	10 (5–15)
Shockable initial rhythm, no. (%)	31 (74)
Number of defibrillations, median (Q1–Q3)	2 (1–4)
Time to ROSC, min, median (Q1–Q3)	26 (19–35)
Presumed cardiac aetiology, no. (%)	34 (81)
Circulatory shock in ER,* no. (%)	18 (42)
Certain pulmonary aspiration, no. (%)	9 (21)
Time to ICU admission, min, median (Q1–Q3)	133 (102–168)
Initial pH, median (Q1–Q3)	7.23 (7.03–7.28)
Initial base excess, mmol/L, median (Q1–Q3)	−10.2 (-14.5 to -6.2)
Initial lactate level, mmol/L, median (Q1–Q3)	6.4 (2.9–11)
Simplified Acute Physiology Score II, mean (SD)	67 (12)
Percutaneous coronary intervention, no (%)	17 (40)
Left ventricular fractional shortening, %, mean (SD)	27 (10)
Left ventricular ejection fraction ≥40 %, n (%)	26 (62)
Wall motion score index, score, median (Q1–Q3)	1.5 (1.1–1.8)
Left ventricular outflow tract velocity time integral, cm, mean (SD)	16.5 (4.3)
Tricuspid annular plane systolic excursion, mm, mean (SD)	18.5 (4.3)
Days in ICU, median (Q1–Q3)	8 (4–12)
Days in hospital, median (Q1–Q3)	15 (7–20)
30 days mortality, no. (%)	15 (36)

*Systolic blood pressure <90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.
ACLS, advanced cardiovascular life support; CPR, cardiopulmonary resuscitation; ER, emergency room; ICU, intensive care unit; Q1–Q3, first to third quartile; ROSC, return of spontaneous circulation.

a significant difference in time to norepinephrine discontinuation between low versus high pro-BNP groups (HR 0.45, 95% CI 0.21 to 0.96), but not between the other groups. We found no significant difference between groups regarding time to negative fluid balance (online supplemental figure 2).

We found no significant association between patients in the high pro-BNP group and demographic variables (table 2).

Oxygen transport and metabolism

Mean VO_2 was stable at approximately 200 mL/min, whereas DO_2 increased from 700 to its peak 950 mL/min during the first 48 hours. Mean SvO_2 was stable at approximately 68%. Mean lactate and $P(v–a)CO_2$ levels were normalised within 24 hours (figure 3).

DISCUSSION

In this study, we found an overall significant increase in CPO, SW and SV during the first 48 hours in patients after OHCA. A stable MAP above 65 mmHg was achieved with initial norepinephrine and fluid infusions that could be reduced over time, even if Ea fell, due to gradually reestablishment of circulatory homoeostasis. We found a significant longer time to norepinephrine discontinuation in patients with high pro-BNP concentration.

The circulatory failure after OHCA has been described as first a reversible myocardial failure that improves over 24 hours, followed by an inflammatory vasodilatation necessitating continued vasopressor support and extra fluid infusion.[3] In acute heart failure most of the cardiac reserves can be mobilised in order to sustain oxygen delivery, and the initial low CPO may indicate exhausted, or nearly exhausted, cardiac reserves due to post-arrest stunning that resolved over the next 48 hours.[15] After 48 hours both the SW and CPO curves flatten, which could indicate a restored heart function. Furthermore, the similarity between the SW and CPO curves indicates that the increase in CPO was not due to an increasing heart rate. Heart rate is temperature dependent but lowering the body temperature to 36°C seemed to have a negligible bradycardic effect. In compliance with the current guidelines MAP were kept above 65 mmHg.[1 13] This was achieved with norepinephrine infusion, which is the preferred vasoactive agent in PCAS.[1 31 32] However, even if calculated Ea fell as a consequence of rising SV and stable blood pressure, this did not lead to an increase in norepinephrine nor fluid infusions. A similar trend in SVR and vasopressor doses has been shown previously.[8 12] This should serve as a reminder that calculated resistance is not an exact measure of vascular tone, nor necessarily a clinical relevant vasoplegia. Thus, we propose that the inflammatory vasodilatation after OHCA is early and resolving, rather than late and emerging.

Microcirculatory failure is central to the circulatory pathogeneses in sepsis.[33 34] It is believed that systemic inflammation-reperfusion injury after OHCA induces a similar circulatory failure.[2] Two small studies using sidestream dark-field (SDF) imaging found reduced microcirculatory flow that improved over the 24 hours after OHCA.[35 36] In presence of an adequate DO_2, an increased $P(v–a)CO_2$ difference is a sign of microcirculatory derangement, and in sepsis shown to correlate with SDF-evaluated microcirculatory flow alterations.[37] Lactataemia in circulatory shock is multifactorial, but during shock commonly regarded as catecholamine-induced hyper-metabolism rather than sign of hypo-perfusion.[38] Regardless of aetiology, lack of lactate clearance is a marker of sustained stressed metabolism, and associated with mortality in critically ill patients.[39] In our study, both

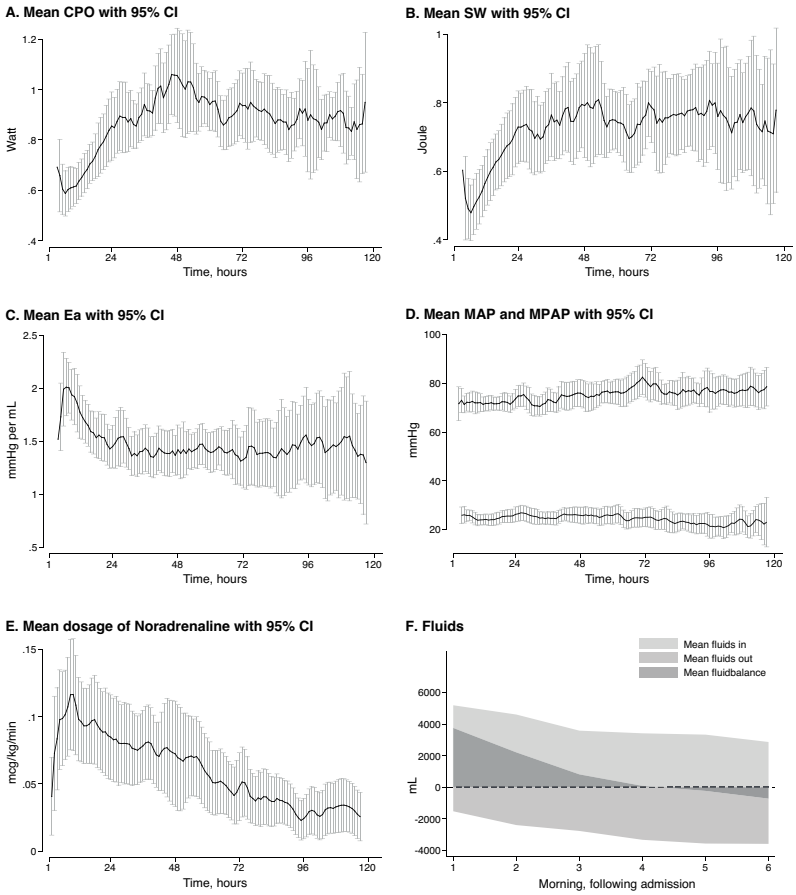

Figure 1 Macrocirculatory variables and circulatory support in 42 patients admitted to ICU after OHCA. (A) Mean cardiac power output with 95% CIs. (B) Mean stroke work with 95% CIs. (C) Mean arterial elastance with 95% CIs. (D) Mean arterial and pulmonary blood pressure with 95% CIs. (E) Mean dosage of norepinephrine with 95% CIs. (F) Mean fluid balance during study period. The mean level of CPO, SW, Ea, norepinephrine dosage at 4 and 48 hours after admission were significantly different ($p<0.05$). The difference in MAP was not significant ($p=0.45$). The graphs were smoothed with a 3 hours moving average. Graphs A, B, C and D were based on the 30 patients with PAC. CPO, cardiac power output; Ea, aortic elastance; ICU, intensive care unit; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; OHCA, out-of-hospital cardiac arrest; SW, stroke work.

lactate and $P(v–a)CO_2$ difference were normalised within 24 hours indicating improved microcirculation.

Taken together, improving macrocirculation and microcirculation with reduced need for circulatory support, and no difference between groups with high versus low inflammation (IL-6 and syndecan-1), it seems that PCAS lacks the self-sustaining inflammation seen in septic shock. In contrast, this study shows that the degree of initial heart failure (expressed by elevated pro-BNP) and not initial cardiac injury (elevated troponin), nor initial inflammation (elevated IL-6, syndecan-1 and CRP), was indicative for longer need of norepinephrine. This difference could not be explained by excess mortality in any of the groups.

Strengths and limitations

Patients in this study were treated at one centre adhering to one protocol, which renders the use of fluid therapy and vasopressors comparable. Furthermore, we measured and assessed the circulatory outcome and interventions in high resolution. However, a single-centre study limits the possible size of the study population, with the risk of making a type II error where significant relationships were missed. Both size and a single centre design reduced the generalisability of the results, however, from a clinical standpoint, the result of this study seemed reasonable. We stratified the groups based on the integral of the biomarker measurements the first 52 hours after the emergency call; acknowledging that a different time

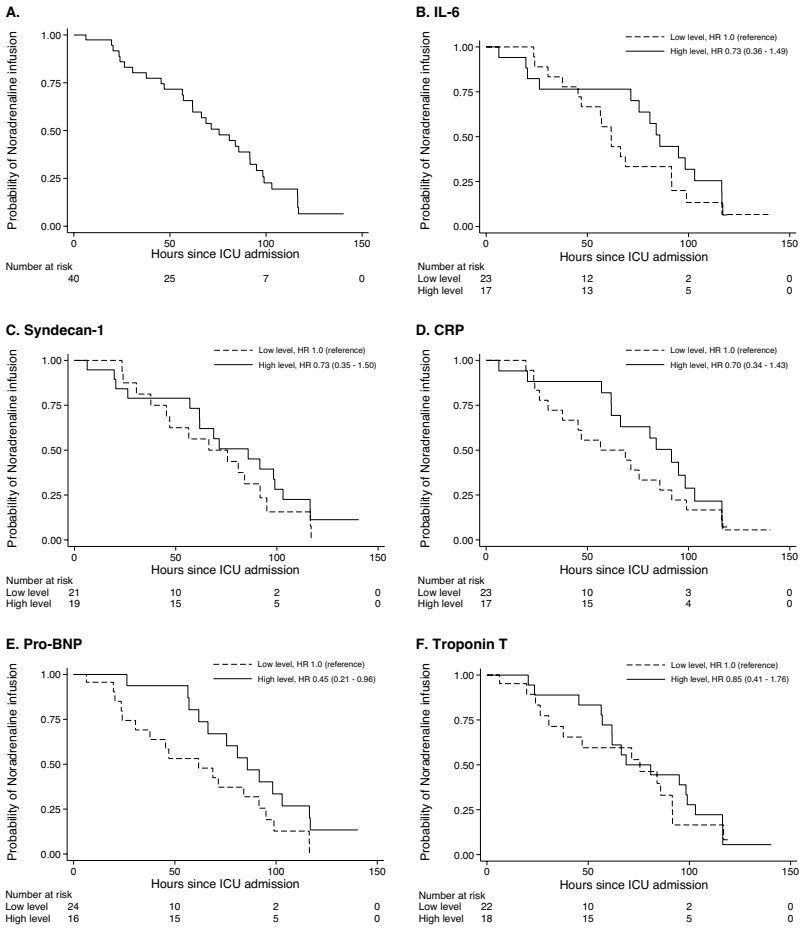

Figure 2 Probability of norepinephrine infusion over time in 42 patients admitted to ICU after OHCA. Kaplan-Meier estimates of the probability of norepinephrine infusion for all patients (A) and stratified by biomarker level (B–F). The HR with 95% CIs was estimated by Cox regression. BNP, brain natriuretic peptide; CRP, C reactive protein; ICU, intensive care unit; IL, interleukin; OHCA, out-of-hospital cardiac arrest.

Table 2 Logistic regression analysis of association between high pro-brain natriuretic peptide and demographic variables

	Univariable analysis
Demographic variables	**OR (95% CI)**
Age, per 5 years	1.22 (0.95 to 1.56)
Charlson Comorbidity Index, point	1.32 (0.97 to 1.80)
Initial shockable rhythm, yes	1.92 (0.43 to 8.69)
Time to ROSC, per 5 min	1.10 (0.89 to 1.37)
Lactate concentration at admission, per mmol/L	0.90 (0.77 to 1.05)
Circulatory shock* in the ER, yes	0.53 (0.14 to 1.96)

*Systolic blood pressure <90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.
ER, emergency room; ROSC, return of spontaneous circulation.

span could have produced a different result. Still, IL-6 and syndecan-1 concentrations peak early and decline rapidly after OHCA, thus the majority of the integral was covered during the first 48 hours.[40 41] Troponin T and pro-BNP showed a similar pattern (online supplemental figure 3). Nonetheless, dichotomising the population based on AUC, rather than a single blood sample, is considered a more robust approach.[29] Finally, sedation affects the need for vasopressors, and we did not examine the impact of late extubation due to respiratory or neurological conditions.[42]

CONCLUSION

In this observational cohort study of 42 patients admitted to ICU after OHCA, the circulatory failure was initially characterised by reduced CPO and SW, however microcirculatory and macrocirculatory homoeostasis was restored

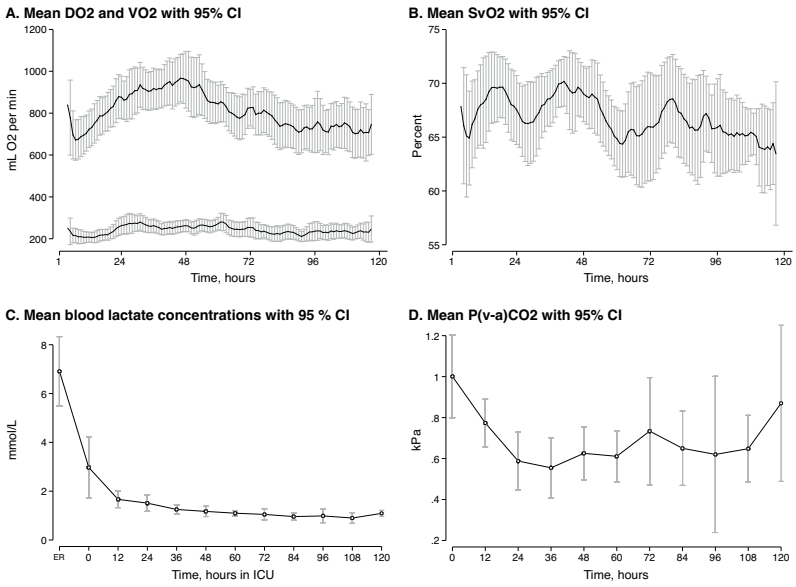

Figure 3 Oxygen transport and metabolic distress variables in 42 patients admitted to ICU after OHCA. (A) Mean global oxygen delivery and consumption with 95% CIs. (B) Mean mixed venous oxygen saturation with 95% CIs. (C) Mean blood lactate concentrations with 95% CIs. (D) Mean venous-to-arterial carbon dioxide difference with 95% CIs. Graph A and B were smoothed with a 3 hours moving average. Graphs A, B and D were based on the 30 patients with PAC. DO_2, oxygen delivery; ER, emergency room; ICU, intensive care unit; OHCA, out-of-hospital cardiac arrest; $P(v–a)CO_2$, venous-to-arterial carbon dioxide difference; SvO_2, mixed venous oxygen saturation; VO_2, oxygen consumption.

within 48 hours. We found that biomarkers indicating acute heart failure, and not inflammation, predicted longer circulatory support with norepinephrine. Taken together, this indicates an early and resolving, rather than a late and emerging vasodilatation.

Contributors HL, DB, NKS and PK included patients, initiated treatment and placed all pulmonary artery catheters in accordance with the study protocol. HL, DB, NKS, PK, TRS and KB supervised the study and patient care daily. HL, ML and TN contributed extensively to the statistical analysis. All authors contributed to interpreting the data and writing the manuscript. All authors have read and approved the final manuscript. HL is the guarantor for the overall content.

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by Regional Committee for Medical and Health Research Ethics, Central Norway Health Region ID: REK Midt, No. 2015/1807 Comatose patients after cardiac arrest.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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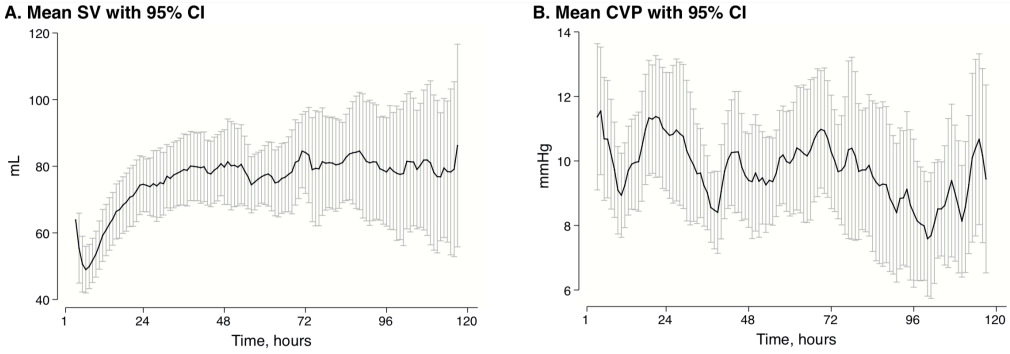
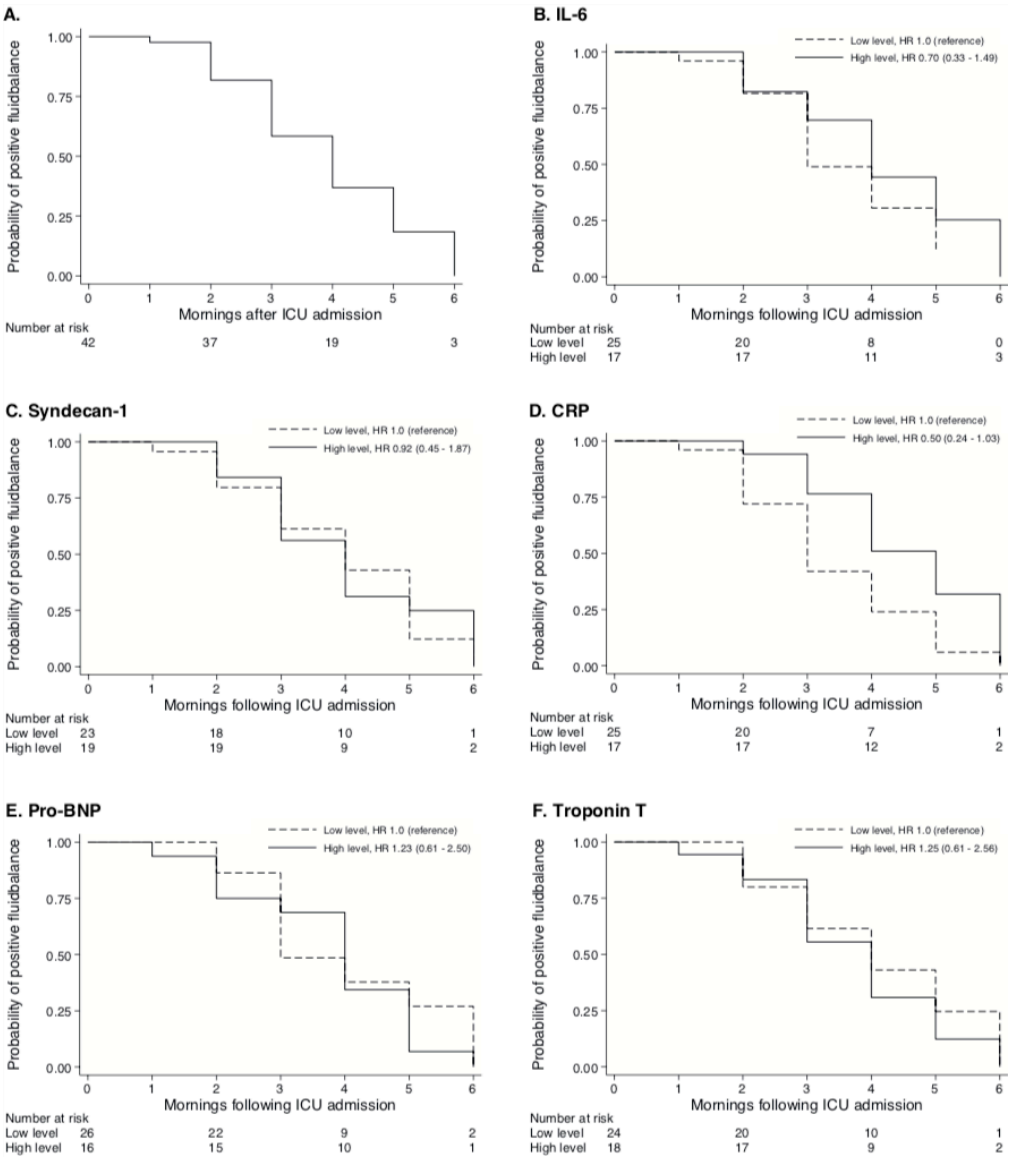
Supplementary Material

Langeland H, Bergum D, Løberg M, Bjørnstad K, Skaug TR, Nordseth T, Klepstad P and Skjærvold NK. The characteristics of circulatory failure after out-of-hospital cardiac arrest: a prospective cohort study. Open Heart. 2022;9(1):e001890



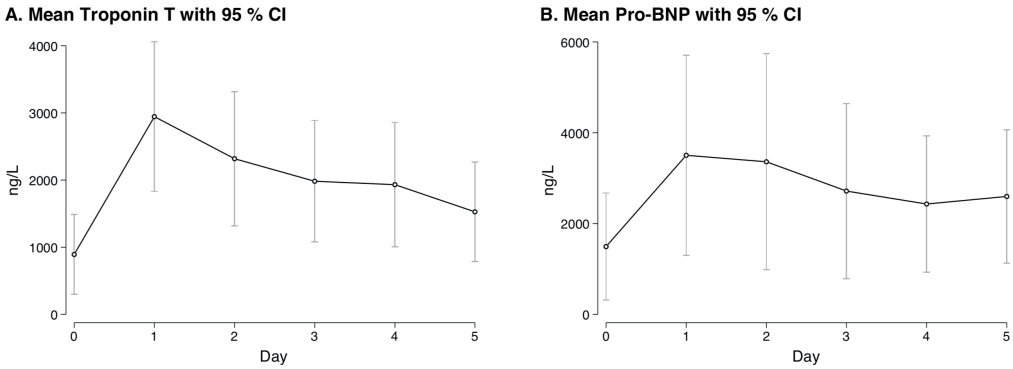
Supplementary figure 1. Macrocirculatory variables in 42 patients admitted to ICU after OHCA.
A. Mean stroke volume with 95% confidence intervals. **B.** Mean central venous pressure with 95% confidence intervals. The graphs were based on the 30 patients with PAC and smoothed with a three-hours moving average.
CI: confidence intervals; CVP: central venous pressure; ICU: intensive care unit; OHCA: out-of-hospital cardiac arrest; SV: stroke volume.



Supplementary figure 2. Probability of positive fluid balance over time in 42 patients admitted to ICU after OHCA.

Kaplan-Meier estimates of the probability of positive fluid balance for all patients (**A**) and stratified by biomarker level (**B–F**). The hazard ratio (HR) with 95% confidence interval was estimated by Cox regression.

BNP: brain natriuretic peptide; CRP: C-reactive protein; HR: hazard ratio; ICU: intensive care unit; IL: interleukin; OHCA: out-of-hospital cardiac arrest.



Supplementary figure 3. Cardiac biomarkers in 42 patients admitted to ICU after OHCA. **A.** Mean Troponin-T levels with 95 % confidence intervals. **B.** Mean Pro brain natriuretic peptide levels with 95 % confidence intervals.
CI: confidence intervals; ICU: ICU: intensive care unit; OHCA: out-of-hospital cardiac arrest; Pro-BNP: pro brain natriuretic peptide.

Supplementary table 1. Demography for all subgroups

Characteristics of patients	IL-6		Syndecan-1		CRP		Pro-BNP		Troponin-T	
	High	Low	High	Low	High	Low	High	Low	High	Low
	n= 7 (41%)	n=25 (59%)	n=19 (45%)	n=23 (55%)	n=17 (41%)	n=25 (59%)	n=16 (39%)	n=26 (61%)	n=18 (43%)	n=24 (57%)
Age, years, mean (SD)	67 (16)	63 (14)	65 (13)	64 (16)	65 (11)	65 (17)	69 (9)	62 (17)	60 (12)	68 (16)
Male sex, no (%)	15 (88)	20 (80)	16 (84)	19 (82)	14 (82)	21 (84)	13 (81)	22 (84)	16 (88)	19 (79)
Body mass index, mean (SD)	30 (10)	26 (4)	29 (10)	27 (4)	28 (10)	27 (4)	26 (4)	29 (9)	26 (4)	29 (9)
CCI, points, median (IQR)	4 (2)	3 (2)	3 (2)	3 (3)	3 (3)	4 (4)	4 (2)	3 (3)	3 (3)	4 (3)
Witnessed cardiac arrest, no. (%)	15 (88)	19 (76)	17 (89)	17 (74)	14 (82)	20 (80)	15 (93)	19 (73)	15 (83)	19 (79)
Bystander CPR, no (%)	16 (94)	21 (86)	17 (89)	20 (87)	14 (82)	23 (92)	14 (88)	23 (88)	14 (77)	23 (96)
Time[1] to ACLS, min, median (IQR)	10 (9)	11 (12)	10 (13)	11 (9)	10 (8)	11 (13)	11 (8)	10 (12)	11 (13)	10 (8)
Shockable initial rhythm, no. (%)	15 (88)	16 (64)	15 (79)	16 (69)	14 (82)	17 (68)	13 (81)	18 (69)	16 (89)	15 (62)
Time[1] to ROSC, min., median (IQR)	26 (16)	26 (16)	26 (16)	24 (16)	29 (13)	23 (16)	26 (20)	24 (15)	30 (13)	20 (15)
Presumed cardiac etiology, no. (%)	15 (88)	19 (76)	16 (84)	18 (78)	15 (88)	19 (76)	15 (93)	19 (73)	17 (94)	17 (71)
Circulatory shock in ER [2], no. (%)	7 (41)	11 (44)	7 (37)	11 (48)	8 (47)	10 (40)	5 (31)	13 (56)	10 (55)	8 (33)
Certain pulmonary aspiration, no. (%)	5 (29)	4 (16)	5 (26)	4 (17)	5 (29)	4 (16)	2 (13)	7 (27)	2 (11)	7 (29)
Time[1] to ICU admission, min, median (IQR)	142(46)	128 (65)	130 (56)	147 (66)	142 (39)	127 (58)	139 (117)	131 (46)	139 (84)	125 (58)
Initial pH, median (IQR)	7.24 (0.09)	7.21 (0.25)	7.24 (0.23)	7.23 (0.27)	7.20 (0.23)	7.24 (0.13)	7.26 (0.26)	7.20 (0.22)	7.24 (0.23)	7.24 (0.23)
Initial base excess, mmol/L, median (IQR)	-7.6 (-5)	-13 (-8)	-11 (-8)	-9 (-8)	-11 (-11)	-9 (-7)	-9 (-7)	-11 (-9)	-11 (-6)	-9 (-10)
Initial lactate level, mmol/L, median (IQR)	5 (4)	8 (8)	7 (9)	5 (7)	6 (8)	6 (6)	4 (6)	7 (8)	5 (5)	7 (9)
SAPS 2, score, mean (SD)	72 (11)	65 (13)	70 (10)	66 (14)	66 (11)	69 (14)	69 (10)	64 (14)	65 (12)	70 (13)
PCI, no (%)	8 (47)	9 (36)	9 (47)	8 (35)	9 (53)	8 (32)	5 (31)	12 (46)	13 (72)	4 (17)

Supplementary table 1. (Continued)

Characteristics of patients	IL-6		Syndecan-1		CRP		Pro-BNP		Troponin-T	
	High	Low	High	Low	High	Low	High	Low	High	Low
	n=17 (41%)	n=25 (59%)	n=19 (45%)	n=23 (55%)	n=17 (41%)	n=25 (59%)	n=16 (39%)	n=26 (61%)	n=18 (43%)	n=24 (57%)
LVEF ≥40 %, n (%)	11 (65)	19 (36)	14 (73)	16 (69)	12 (70)	18 (72)	9 (56)	21 (80)	14 (77)	16 (66)
LVFS, %, mean (SD)	25 (11)	29 (10)	27 (11)	28 (11)	25 (11)	29 (10)	22 (11)	31 (8)	29 (9)	26 (11)
WMSI, score, median (IQR)	1.3 (0.8)	1.6 (0.7)	1.6 (0.7)	1.4 (0.7)	1.3 (0.8)	1.6 (0.7)	1.8 (0.5)	1.2 (0.8)	1.4 (0.6)	1.8 (0.85)
LVOT-VTI, cm, mean (SD)	16 (5)	17 (4)	15 (5)	17 (4)	16 (4)	17 (5)	14 (3)	18 (4)	17 (4)	16 (4)
TAPSE, mm, mean (SD)	16 (4)	20 (4)	18 (4)	19 (4)	17 (4)	20 (5)	17 (4)	20 (4)	19 (4)	18 (4)
Days in ICU, median (IQR)	11 (8)	6 (7)	10 (12)	7 (9)	10 (7)	5 (9)	12 (7)	6 (8)	11 (8)	6 (9)
Days in hospital, median (IQR)	19 (11)	11 (10)	16 (17)	12 (17)	15 (17)	13 (16)	18 (20)	11 (15)	16 (19)	12 (15)
30-days mortality, no. (%)	4 (23)	11 (44)	7 (37)	8 (35)	6 (35)	9 (36)	5 (31)	10 (38)	4 (22)	11 (46)

[1] Time from emergency call to event.
[2] Systolic blood pressure <90 mmHg or in need of fluids and/or vasopressors to maintain systolic blood pressure >90 mmHg.
ACLS: advanced cardiovascular life support; CCI: Charlson comorbidity index ; CPR: cardiopulmonary resuscitation; ER: emergency room; IQR: interquartile range; LVEF: left ventricular ejection fraction; LVFS: left ventricular fractional shortening; LVOT-VTI: left ventricular outflow tract velocity time integral; PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation; SAPS: Simplified Acute Physiology Score; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; WMSI: wall motion score index.

Supplementary table 2. Echocardiographic evaluation during first 24 hours

Measurements	n = 38
Left ventricular posterior wall thickness, mm, mean (SD)	11 (2)
Septal thickness, mm, mean (SD)	11 (2)
Left ventricular end-diastolic dimension, mm, mean (SD)	50 (10)
Left ventricular end-systolic dimension, mm, mean (SD)	37 (12)
Left ventricular ejection fraction, n (%)	
<20 %	2 (5)
20 – <30 %	3 (8)
30 – <40 %	7 (18)
40 – <50 %	13 (35)
50 – <60 %	11 (29)
≥60 %	2 (5)
Left ventricular fractional shortening, %, mean (SD)	27 (10)
Wall motion score index, score, median (Q1–Q3)	1.5 (1.1-1.8)
Left ventricular outflow tract velocity time integral, cm, mean (SD)	16.6 (4.3)
Right ventricular basal diameter, mm, mean (SD)	39.4 (6.4)
Tricuspid annular plane systolic excursion, mm, mean (SD)	18.5 (4.3)
ST-elevated myocardial infarction	21 (55)
Non-ST-elevated myocardial infarction	1 (2)
Old myocardial infarction, n (%)	6 (16)
Valvular pathology [1, 2]	13 (34)

[1] Excluding mild tricuspid valve insufficiency.
[2] One mild aortic valve stenosis; one moderate aortic valve insufficiency; six mild and one moderate mitral valve insufficiency; three moderate and one severe tricuspid valve insufficiency.
SD: standard deviation; Q1–Q3: first to third quartile.

Supplementary text 1.

Appendix to blood sample handling and analyzes

The blood samples were first gently mixed; then vertically placed for 30 minutes in ambient temperature; and finally centrifuged at 2200 g for 10 minutes. The supernatant (EDTA-plasma) was frozen to –80 °C within 1 hour from time of sampling.

C-reactive protein, Troponin T and Pro-Brain natriuretic peptide were analyzed together with the routine blood samples at St. Olav's University Hospital's medical laboratory.

Plasma levels of interleukin 6 were analyzed with Bio-Plex Pro™ Human Cytokine 27-plex Assay (Bio-Rad Laboratories, Hercules, CA) by bioengineers according to the manufactures.

Plasma levels of syndecan-1 were measured by enzyme immunoassays in duplicate using commercially available antibodies (R&D Systems and Agilent, Minneapolis, MN) in a 384 format using a combination of a CyBi-SELMA pipetting robot (Analytik Jena, Germany) and an automatic washer-dispenser (BioTek, Winooski, VN). Absorption was read at 450 nm with wavelength correction set to 540 nm using an ELISA plate reader (BioTek). Intra- and inter-assay coefficients of variation were <10 % for all enzyme immunoassays.

Measurements of interleukin 6 and syndecan-1 under the lower limit of detection were set to 0.01.

Appendix

"All models are approximations. Essentially, all models are wrong, but some are useful. The approximate nature of the model must always be born in mind."

- George E. P. Box

Appendix 1: Charlson comorbidity index

Points	Condition
0	No comorbid conditions
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease with mild or no residua, or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease without portal hypertension (includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 years from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)
x	For each decade >40 years of age, a score of 1 is added to the above score.

ECG: electrocardiogram; TIA: transient ischemic attack.

Validation of a combined comorbidity index.

Charlson M, Szatrowski TP, Peterson J, Gold J. J Clin Epidemiol 1994 Nov;47(11):1245-1251.

Appendix 2. Simplified acute physiology score II

Points *	0	1	2	3	4	5	6	7	8	9	10	11	12	13	15	16	17	18	26
Age, years	<40							40–59					60–69		70–74	75–79		≥80	
Chronic disease	Nil									Ca. cum met.	Hem.ca						AIDS		
Type of admission	Sched. surg						Medical		Emerg. surg.										
Heart rate, bpm	70–119		40–69		120–159			>160				<40							
Systolic BP, mmHg	100–199		>200			70–99								<70					
Temperature, °C	<39			>39															
PaO_2/FiO_2, kPa							>26.6			13.3 – 26.6		<13.3							
Urine output, ml/24 hrs.	>1000				>500							<500							
Urea, mmol/L	<10						10–29.6				>29.6								
WBC, $x10^3/mm^2$	1–20			>20									<1						
Potassium, mmol/L	3–4.9			<3 or >5															
Sodium, mmol/L	125–144	>145				<125													
Bicarbonate, mmol/L	>20			15–19			<15												
Bilirubin, µmol/L	<68.4				68.4–102.6					>102.6									
GCS ‡	14–15					11–13		9–10						6–8					<6

* Score based on the worst observation during the first 24 hours of intensive care.
‡ If patient is sedated and intubated, GCS is based on last score before intubation.
AIDS: acquired immunodeficiency syndrome; bpm: beats per minute; Ca. cum met.: metastatic cancer; Emerg. surg.: emergency surgery; GCS: Glasgow coma scale; Hem. Ca: hematologic cancer; Sched.surg.: scheduled surgery; hrs: hours; WBC: white blood cell count.

From:
A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study.
Le Gall JR, Lemeshow S, Saulnier F. J Am Med Assoc 1993;270(24):2957-2963.

Appendix 3: Modified clinical pulmonary infection score

Points *	0	1	2
Temperature, ℃	36.5 – 38.4	38.5 – 38.9	<36 or >39
WBC, $x10^3/mm^2$	4.0 – 11.0	<4.0 or >11.0	-
PaO_2/FiO_2, kPa	>31.9 or ARDS ‡	-	<31.9 and no ARDS ‡
Chest x-ray	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate
Tracheal secretions	Absent	Non-purulent	Purulent

* If positive microbiological culture of tracheal aspirate add +2 points

‡ ARDS defined as PaO_2/FiO_2 ≤26.6 kPa, PAOP ≤18 mmHg and acute bilateral infiltrates on chest x-ray.

ARDS: acute respiratory distress syndrome; PAOP: pulmonary artery occlusion pressure; WBC: white blood cell count.

Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription.

Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Am J Respir Crit Care Med 2000 Aug;162(2 Pt 1):505-511.

Appendix 4: Sequential organ failure assessment

Points	0	1	2	3	4
Respiration *					
PaO_2/FiO_2, kPa	≥53.3	<53.3	<40	<26.7 & respiratory support	<13.3 & respiratory support
SaO_2/FiO_2, %	≥302	221–301	142–220	67–141	<67
Circulation					
Hypotension	MAP ≥70	MAP <70	Dopamine ≤5 or Dobutamine (any dose)	Dopamine >5 or Noradrenaline ≤0.1	Dopamine >15 or Noradrenaline >0.1
Hepatic					
Bilirubin, µmol/L	<20	20–32	33–101	102-204	>204
Renal					
Creatinin, µmol/L	<110	110–170	171–299	300–440	>440
Urine output, ml/24 hrs				<500	<200
Coagulation					
Platelets, $x10^3$/ L	≥150	<150	<100	<50	<20
CNS ‡					
GCS	15	13–14	10–12	6–9	<6

* 2 points are max if no respiratory support is needed. ‡ if patient is sedated and intubated, GCS is based on the last score before intubation.

CNS: central nervous system; GCS: Glasgow coma scale; hrs: hours; MAP: mean arterial pressure.

The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.

Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. Intensive Care Med 1996 Jul;22(7):707-710.

Appendix 5: Cerebral performance categories

CPC 1	Good cerebral performance (normal life)	Conscious, alert, able to work and lead a normal life. Might have mild neurologic or psychological deficit (mild dysphasia, non-incapacitated hemiparesis or cranial nerve abnormalities).
CPC 2	Moderate cerebral disability (disabled but independent)	Conscious, sufficient cerebral function for independent activities of daily life (dress, food preparation, able to travel by public transportation). Able to work in sheltered environment. May have hemiplegia, seizures, ataxia, dysarthria, dysphasia or permanent memory or mental changes.
CPC 3	Severe cerebral disability (conscious but disabled and dependent)	Conscious, dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). Has at least limited cognition. This category ranges from ambulatory state to severe dementia or paralysis.
CPC 4	Coma or vegetative state (unconscious)	Any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5	Brain death (certified brain dead or dead by traditional criteria)	Apnea, areflexia, EEG silence, etc.

CPC: Cerebral performance categories; EEG: electroencephalogram

Assessment of outcome after severe brain damage.
Jennett B, Bond M. Lancet 1975 Mar 01;1(7905):480-484.

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