Circulatory Failure and Outcome in Out-of-Hospital Cardiac Arrest

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DOCTORAL DISSERTATION

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Abstract

Circulatory failure is considered one of the entities of the post cardiac arrest syndrome contributing to poor outcome. It is reported at 15-70% of all patients successfully resuscitated from out-of-hospital cardiac arrest (OHCA). The pathophysiologic mechanism is attributed to limitation of cell metabolism due to inadequate supply of oxygen, caused by pump or conduction failure within the cardiovascular system. The term, however, remains poorly defined and no general consensus on definition exists. Due to the heterogeneity in definition and mechanism, the association with outcome for circulatory failure in cardiac arrest varies, and is partly conflicting. In this thesis we investigate four different surrogate measures of circulatory failure and their association with outcome after out-of-hospital cardiac arrest.

Paper I: We conducted a post hoc analysis of adult, unconscious survivors of out-of-hospital included in the TTM-1 trial, to investigate lactate, a marker of anaerobic metabolism, as a predictor of short-term survival. 877 patients had admission lactate sampled and were included in analyses. Lactate at admission and 12 hours were independently associated with 30-day survival in a model adjusted for known predictors of survival after out-of-hospital cardiac arrest. Estimations of area under the receiver operator curve indicate a poor precision for predicting short time survival, limiting the clinical utility for lactate metrics as a sole predictor of outcome.

Paper II: Copeptin, physiologically associated with vasoregulatory status, was analyzed as a marker of severity of circulatory failure, in this post hoc analysis of 690 patients included in the TTM-1 biobank sub study. Copeptin measured at 24 hours was found to be independently associated with 30-day survival, circulatory etiology of death and cardiovascular deterioration.

Paper III: In this retrospective registry study of 4004 adult, unconscious patients resuscitated from OHCA, a composite definition of circulatory shock (systolic blood pressure < 90 mmHg, or use of inotropes/vasoactive agents, or clinical signs of hypoperfusion), compared to no circulatory shock on admission was associated with worse odds of good neurological outcome at hospital discharge in an analysis adjusted for baseline comorbidity and predictors of outcome.

Paper IV: Patients with moderate vasopressor support (defined as mean arterial pressure < 70 mmHg and/or adrenalin/noradrenaline dose □0.25 µg/kg/min) treated with target temperature management at 33ºC had higher incidence of 6-month mortality compared to patients treated with normothermia, in a post hoc analysis of 1861 OHCA patients included in the TTM-2 trial. No difference in mortality was detected with temperature intervention in patients with no- or high vasopressor support. The increase in mortality seems to be driven by an increase in 30-day incidence of non-neurological death in patients treated at 33ºC, compared to normothermia, in the moderate vasopressor support group, while no difference in etiology of death was detected for intervention in the no-, and high vasopressor support group.

Conclusion: Circulatory failure after OHCA is associated with outcome, however, the mechanism is complex and probably contains multiple pathways.

Key words: Cardiac arrest, Temperature management, Outcome, Shock, Copeptin, Lactate, Circulatory support

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“Success is stumbling from failure to failure with no loss of enthusiasm” W. Churchill

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List of publications

The thesis is based on the following papers, which are referred to in text by their Roman numerals.

I. **Düring J**, Dankiewicz J, Cronberg T, Hassager C, Hovdenes J, Kjaergaard J, Kuiper M, Nielsen N, Pellis T, Stammet P, Vulto J, Wanscher M, Wise M, Åneman A, Friberg H. Lactate, lactate clearance and outcome after cardiac arrest: A post-hoc analysis of the TTM-Trial. Acta Anaesthesiol Scand. 2018 Nov;62(10):1436-1442. doi: 10.1111/aas.13172. Epub 2018 Jun 21. PMID: 29926901.

II. **Düring J**, Annborn M, Cronberg T, Dankiewicz J, Devaux Y, Hassager C, Horn J, Kjaergaard J, Kuiper M, Nikoukhah HR, Stammet P, Undén J, Wanscher MJ, Wise M, Friberg H, Nielsen N. Copeptin as a marker of outcome after cardiac arrest: a sub-study of the TTM trial. Crit Care. 2020 Apr 28;24(1):185. doi: 10.1186/s13054-020-02904-8. PMID: 32345356; PMCID: PMC7189642.

III. **Düring J**, Annborn M, Dankiewicz J, Dupont A, Forsberg S, Friberg H, Kern K.B, May T.L, McPherson J, Patel N, Seder D.B, Stammet P, Sunde K, Søreide E, Ullén S, Nielsen N. Influence of circulatory shock at hospital admission on outcome after out-of-hospital cardiac arrest

IV. **Düring J,** Annborn M, Cariou A, Chew M.S, Dankiewicz J, Friberg H, Haenggi M, Haxhija J, Jakobsen J.C, Halvor Langeland H, Taccone F.S, Thomas M, Ullén S, Wise M.P, Nielsen N. Influence of temperature management at 33ºC versus normothermia on survival in patients with vasopressor support after out-of-hospital cardiac arrest: A post-hoc analysis of the TTM-2 trial.

Publications not included in thesis

Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, Rylander C, Wise MP, Oddo M, **Düring J** et al: Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. New England Journal of Medicine 2021, 384(24):2283-2294.

Lybeck A, Cronberg T, Borgquist O, **Düring J.P**, Mattiasson G, Piros D, Backman S, Friberg H, Westhall E: Bedside interpretation of simplified continuous EEG after cardiac arrest. Acta Anaesthesiol Scand 2020, 64(1):85-92.

Chew MS, Ihrman L, **Düring J**, Bergenzaun L, Ersson A, Undén J, Ryden J, Akerman E, Larsson M: Extravascular lung water index improves the diagnostic accuracy of lung injury in patients with shock. Crit Care 2012, 16(1): R1.

Bergenzaun L, Ohlin H, Gudmundsson P, **Düring J**, Willenheimer R, Chew MS: High-sensitive cardiac Troponin T is superior to echocardiography in predicting 1-year mortality in patients with SIRS and shock in intensive care. BMC Anesthesiol 2012, 12:25.

Bergenzaun L, Gudmundsson P, Ohlin H, **Düring J**, Ersson A, Ihrman L, Willenheimer R, Chew MS: Assessing left ventricular systolic function in shock: evaluation of echocardiographic parameters in intensive care. Crit Care 2011, 15(4): R200.

Abbreviations

ADH: Anti Diuretic Hormone

ALS: Advanced Life Support

ATP: Adenosine Triphosphate

AUROC: Area Under the Receiver Operator Curve

AVP: Arginine Vasopressin

CI: Confidence Interval

CPC: Cerebral Performance Category

GCP: Good Clinical Praxis

CvDC: Cardiovascular Deterioration Composite

DNR: Do Not Resuscitate

eCvSOFA: Extended Cardiovascular Sequential Organ Failure Assessment

EMS: Emergency Medical Systems

ERC: European Resuscitation Council

ESICM: European Society of Intensive Care Medicine

High-VS: High Vasopressor Support on hospital admission

HR: Hazard Ratio

ICU: Intensive Care Unit

IHCA: In-Hospital Cardiac Arrest

IQR: Interquartile range

LBBB: Left Bundle Branch Block

MAP: Mean Arterial Pressure

Moderate-VS: Moderate Vasopressor Support on hospital admission

mRS: Modified Rankin Score

No-VS: No Vasopressor Support on hospital admission

OR: Odds Ratio

OHCA: Out-of-Hospital Cardiac Arrest

PCAS: Post Cardiac Arrest Syndrome

PEA: Pulseless Electrical Activity

ROSC: Return of Spontaneous Circulation

SOFA: Sequential Organ Failure Assessment

STEMI: ST-segment Elevation Myocardial Infarction

TTM: Targeted Temperature Management

VF: Ventricular Fibrillation

VF: Ventricular Tachycardia

WLST: Withdrawal of Life Sustaining Therapies

Introduction

Cardiac arrest

A decrease in cardiac output below critical levels results in insufficient oxygen delivery to support vital organ functions and ultimately life. Cardiac arrest could be viewed as a very rapid reduction in cardiac output. Most scientific publications refer to cardiac arrest according to the Utstein style criteria, absence of signs of circulation [1], usually presenting as an unresponsive person with no/abnormal breathing (and for experienced personnel, absence of pulses) [2].

Cardiac arrest events are traditionally categorized according to location of event in out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) [1,3]. The logic for this classification is perceived differences in epidemiology, process of care and outcome, however, this is based on low level and partially conflicting evidence [4-9].

Furthermore, initial first documented rhythm, present after a monitor or defibrillator is connected to the patient after cardiac arrest, is used to characterize the event as ventricular fibrillation (VF), ventricular tachycardia (VT), pulseless electrical activity (PEA) or asystole. The different initial rhythms carry significantly different survival rates [10,11]. Commonly rhythm is dichotomized as shockable (VT, VF) or non-shockable (Asystole and PEA). An initial shockable rhythm may deteriorate to non-shockable as time progress [12] and, conversely a non-shockable rhythm may convert to a shockable rhythm as resuscitation progress [13].

Pathophysiology, treatment, patient characteristics and outcome [14] of cardiac arrest may be very different depending on etiology. According to the Utstein criteria for reporting [1] cause of arrest in OHCA is categorized as medical (including cardiac cause), traumatic, drug overdose, drowning, electrocution and asphyxia. The majority of patients classified as having a medical cause of arrest, primarily have a cardiac etiology [15]. Cardiac arrest in this thesis refers to OHCA of medical etiology in adult patients.

Utstein-style reporting

To support a uniform reporting system in cardiac arrest research, a consensus statement for defining key elements of cardiac arrest epidemiology and care was made by an international multidisciplinary expert group, at the Utstein abbey, Norway 1990 [16]. Originally, only non-Emergency Medical Services (EMS) witnessed cardiac arrests of presumed cardiac cause with ventricular fibrillation was covered by the statement. In 2004, the Utstein reporting template was revised and expanded to include all EMS treated and in-hospital cardiac arrests (IHCA) [17]. The current version (2015) of reporting guidelines consists of 5 domains (System, Dispatch, Patient, Process and Outcome) that contain core- and supplemental elements of defined variables, for out-of-hospital cardiac arrest only [1]. A separate Utstein template is used for IHCA since 2019 [3]. In this thesis and in the papers supporting it, wherever possible, Utstein-style variables have been used to define core elements of cardiac arrest care including: 1) Return of spontaneous circulation (ROSC), defined as a clinical assessment that shows signs of life comprising a palpable pulse or generating a blood pressure; 2) Outcome documented as survival and neurologic function recorded at 30-days or hospital discharge. Neurologic recovery is assessed according to Cerebral Performance Category (CPC) [18], or modified Rankin score (mRS) [19]. CPC is a 5-point ordinal scale ranging from 1 (good cerebral performance) to 5 (dead), and mRS is a 7- point scale ranging from 0 (no symptoms) to 6 (dead). Neurologic recovery is commonly dichotomized as good or poor with a cut-off for good outcome at CPC<3 or mRS<4.

Postcardiac arrest syndrome

Originally described by Negovsky [20], the stereotypical pathologic events following cardiac arrest has been termed *the post cardiac arrest syndrome* (PCAS) [21]. It accounts for most of the mortality/morbidity following ROSC, and the severity of PCAS is dependent on the interaction of patient characteristics with aggregated ischemic insult during no/low-flow duration [22]. Although significant overlap and interaction exists, the PCAS, by the ILCOR definition [21] can be viewed to have four key components: 1) Systemic ischemia/reperfusion response; 2) Hypoxic ischemic brain injury; 3) Myocardial dysfunction; 4) Persistent precipitating pathology.

Systemic ischemia/reperfusion response

In a highly simplified model, the systemic ischemia/reperfusion response can be divided in two major phases. No flow induced ischemia causes a rapid intracellular adenosine triphosphate (ATP) depletion and subsequent ion channel dysfunction

with intracellular oedema due to increased Na^+ permeability. A build-up of interstitial potassium follows, triggering membrane depolarization and opening of voltage gated Ca^{2+} channels in the sarcoplasmic reticulum, and loss of mitochondrial membrane potential. These derangements stop further ATP regeneration, induce intracellular lactic-acidosis and activate apoptosis. Initiation of the second stage is dominated by oxidative stress during reperfusion, caused by the formation of radical oxygen species (ROS) and reduction of antioxidant defenses. This inactivates cytochromes and initiates membrane lipid peroxidation [23]. These changes aggravate energy depletion and increased cellular ion permeability, further promoting cellular death [23,24]. ROS mediated cellular injury also triggers widespread endovascular damage, initiating complement, inflammatory [25,26] and coagulation [27] cascade systems leading to microcirculatory failure, potentiation of endothelial injury and the sequestration of activated neutrophils in vital organs, potentially resulting in a sepsis-like multiorgan failure [26,28].

Hypoxic ischemic brain injury

The brain function requires about 20-25% of cardiac output and lacks nutritional stores leaving it especially vulnerable to ischemia [21,29]. Loss of consciousness and isoelectric EEG usually occur within 20-30 seconds after cessation of blood flow [30,31].

The initial ischemic event accounts for the major burden of sustained neuronal injury in cardiac arrest, however, a substantial degree is also attained after restoration of cerebral oxygen delivery [32]. The cerebral hypoperfusion, following an initial hyperemic phase, is believed to be caused by a decrease in nitric oxide, impairing cerebral autoregulation (The innate physiologic mechanism to keep cerebral blood flow constant over a wide range of blood pressures) [33,34].

Impaired blood brain barrier function due to endothelial dysfunction and microcirculatory derangements lead to fluid extravasation, increased plasma viscosity, further increasing vascular resistance [35]. The extravasation and concomitant cerebral oedema are especially problematic within the confines of the intracranial vault, causing increased intracranial pressure and a further decrease in cerebral blood flow, occasionally escalating to cerebral herniation. Additional neuronal injury after reperfusion is caused by release of excitatory neurotransmitters [36].

Cerebral blood flow, and indirectly cerebral oxygen delivery, can also be affected by ventilatory status after cardiac arrest. Hypercapnia decreases cerebral vascular resistance, increasing blood flow and intracranial pressure, while opposite reactions with potential cerebral ischemia is triggered by hypocapnia [37-39]. Hypercapnia is also associated with increased oxygen demand and increased levels of neuroexcitatory transmitters [40].

Fever control after OHCA, according to conservative criteria (core body temperature < 37.8°C), occurred in approximately 50% of patients in the

normothermia arm in the TTM-2 trial [41]. Hyperthermia has been shown to be associated with increased cerebral metabolism, a decrease in blood brain barrier integrity, increasing cerebral oedema/intracranial pressure, increase neuroexcitatory transmitters and disrupted autoregulation [21,42], possibly adding to morbidity and mortality in cardiac arrest.

Myocardial dysfunction

Cardiovascular failure accounts for approximately 25% of all deaths in successfully resuscitated patients after OHCA [43-46]. Circulatory cause of death typically occurs within the first 3 days, distinguishing it from the later onset of neurological mode of death [44,46].

Even in the absence of occlusive coronary ischemia, myocardial stunning after cardiac arrest is common. It is characterized by the onset of left ventricular systolic and diastolic dysfunction, peaking within 8 hours, and usually resolves completely in 72 hours [47,48]. Reduced preload due to vasodilatory failure and inflammatory mediated extravasation [26], in combination with myocardial dysfunction decrease stroke volume, aggravating circulatory failure and reduce oxygen delivery [49].

Persistent precipitating pathology

Events triggering cardiac arrest depend on the population studied. Acute coronary syndrome, pulmonary embolism, respiratory failure, sepsis, hemorrhage, stroke, intoxication are all possible etiologies of cardiac arrest, with ongoing pathophysiological implications for treatment and outcome.

In an American single center retrospective analysis, acute coronary syndrome was presumed to be the precipitating etiology in 16% of events, followed by respiratory failure in 12%, and intoxication in 11%. Two or more causes were identified in 17% of patients [50]. In a population of OHCA with a unknown or presumed cardiac cause of arrest, acute coronary syndrome is more prevalent, with ST-elevation segment myocardial infarction (STEMI) in 40% of patients [41], and significant coronary lesions in patients with non-STEMI in approximately 40% of remaining patients [51,52].

Epidemiology of cardiac arrest

According to estimations, OHCA accounts for 3.3 million lost years of potential life annually, and is the most frequent cause of death for males in the USA [53].

The incidence of OHCA has been reported at 89 (Europe) and 141 (USA) cases per 100,000 person years and cardiopulmonary resuscitation (CPR) is started in 60-70%

of cases [54-56]. The data is not uniform within regions and span a wide range. This is possibly explained by differences in population characteristics, culture, EMS, and quality assurance systems. The true incidence of OHCA is, however, unknown and likely underreported because available data on incidence is mostly based on reporting by the EMS systems. For multiple reasons e.g., culture, religion, *Do Not Resuscitate* (DNR) orders, unwitnessed cardiac arrest, ethical reasons etc., EMS systems may not be alerted to the patient suffering cardiac arrest.

Characteristics and outcome vary widely between regions depending on population, geography and EMS/healthcare systems. In Europe and the USA, roughly 65 % of OHCA patients with attempted CPR are men and in their mid to late sixties [54-56], 25% present without any previous symptoms [57]. About 70 % of events occur at home, and 50-70 % are witnessed [54-56]. Ninety percent of OHCA are classified as of medical etiology [54].

Conditions associated with medical cause of cardiac arrest in younger patients are more dependent on structural heart disease (hypertrophic cardiomyopathy, coronary artery anomalies) while the majority of the older population suffer from coronary atherosclerosis [58], previous heart disease [59], and lower socio-economic status [60]. A minority, 5-10 %, of OHCA, occurs in absence of any of these risk factors [61].

In a general OHCA population any return of spontaneous circulation (ROSC) after OHCA has been reported to be approximately 30% [54,62] and survival to hospital discharge 8-12% [54,55,62-64]. These numbers, as with risk factors and incidence, are highly dependent on multiple factors including sex [65,66], initial arrest rhythm [11,67-69], comorbidities [70-72], location [73,74] , socio-economic status [75,76], ethnicity [77], healthcare and EMS systems [78]. Hospital survival with good neurological outcome based on all OHCA where CPR is started has been reported at 3-9% [63,79].

Thirty-day survival after OHCA in Sweden has more than doubled from about 4% at the turn of the millennium to 11% 2020, however, survival has not significantly increased in the last ten years [80]. When categorizing patients according to first documented rhythm the trend in survival over the past 20 years is even more striking: VT/VF from 14 to 34%, PEA 0.5 to 5.7%, Asystole 0.8 to 1.5 % [80]. The increase in survival could primarily be attributed to prehospital factors reducing no flow/low flow time, e.g., bystander CPR, dispatch assisted CPR, time to defibrillation, and EMS response time [81-85].

Chain of survival

Survival after cardiac arrest is dependent on a series of interlinked interventions illustrated conceptually as the *Chain of survival* originally introduced by Cummins et al 1991, later to be revised to the current version in the 2005 European Resuscitation guidelines (Figure 1) [86]. The chain analogy focuses on early recognition of cardiac arrest with activation of EMS systems, reducing no-flow with rapid start of high-quality CPR and advanced life support (ALS) with emphasis on early defibrillation whenever possible, and finally mitigating injuries by post cardiac arrest care. All links of the chain of survival are, however, not equal since the relative contribution on survival rapidly diminishes for each step [87]. In this brief summary the *Chain of survival* refers to the European resuscitation council definition and guidelines, although, similar concepts are available in other regions.

Figure 1
The Chain of survival, conceptual illustration of survival after cardiac arrest dependent on critical interlinked interventions. © European Resuscitation Council, reprinted with permission.

Guidelines covering the *Chain of survival* are issued by the major governing bodies for resuscitation care (in Europe, the European Resuscitation Council) based on International Liaison Committee on Resuscitation's (ILCOR) Consensus on Science and Treatment Recommendations (CoSTR). The guidelines are updated every five years.

Early recognition

Cardiac etiology is the most common cause of OHCA [14], most cardiac diseases can, however, be treated. With an overall survival of approximately 10% early recognition of cardiac disease to prevent OHCA is paramount [54,56,88]. The most common conditions associated with sudden cardiac death are: coronary heart

disease, electrical heart disease, congenital heart disease, hypertrophic cardiomyopathy, dilatated cardiomyopathy and valvular heart disease [89,90]. Most sudden cardiac death is preceded by chest pain, dyspnea, syncope, cold sweats or palpitations [57,91-97]. Prevention is mainly focused on treating underlying condition that may contribute to cardiac arrest, and sometimes include anti-arrhythmic drugs, implantable cardioverters, ablation or surgery [98,99]. Observational evidence suggests that over 90% of patients experience severe warning symptoms within 24 hours of cardiac arrest, and that alerting EMS in response to these symptoms is associated with a fivefold increase in survival [91] underlining the importance of early recognition.

Advanced life support algorithm

Early CPR includes high quality chest compression and ventilation, with the purpose of maintaining some extent of organ perfusion during treatment, and is associated with increased survival [81,100]. *Early defibrillation* aims to terminate the cardiac arrest in shockable rhythms, and increases favorable outcome [101].

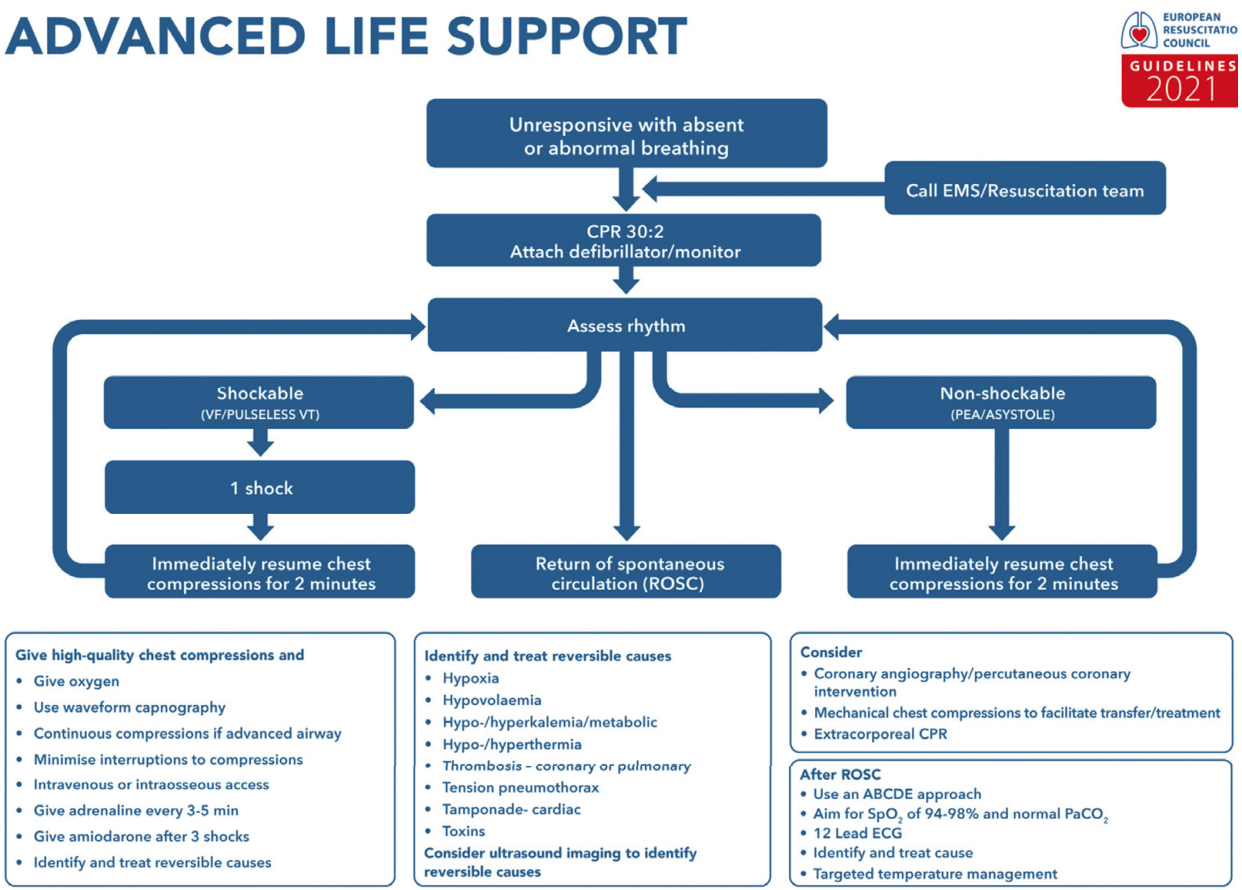

Figure 2
The 2021 European resuscitation council ALS algorithm. © European resuscitation council, reprinted with permission.

Advanced life support, sometimes interchangeably referred to as *advanced cardiac life support* is a widely and clinically accepted treatment algorithm encompassing *early CPR* with *early defibrillation*, drugs and identification/treatment of reversable causes of arrest in a structured and timely manner (Figure 2). The ultimate goal of ALS is to minimize cell death by reduced oxygen delivery and restore spontaneous circulation urgently. The evidence supporting the full concept [102,103] is low. Vasopressor and antiarrhythmic agents used in the ALS algorithm, have been shown only to increase frequency of ROSC and/or survival, but not favorable neurologic outcome [104-106].

Post cardiac arrest care

Post cardiac arrest care starts immediately after ROSC, with the general purpose of preventing or mitigating secondary injury. It largely applies to adult unconscious survivors of cardiac arrest from medical etiology, although many of the treatment principles applies to other patient categories and critical care in general.

At present, no specific clinically applied post-resuscitation therapy has been shown to improve outcome after cardiac arrest, and guidelines are mostly based on low/moderate certainty evidence, expert consensus, or extrapolated from other patient populations. Some of the key elements targeted outside the scope of general critical care principles are reperfusion, temperature management and neurologic prognostication.

General critical care management

The management of cardiac arrest survivors in the intensive care unit (ICU) is similar with that of other critically ill patients and follows the same principles, some of which have been studied in more detail for this category of patients are discussed below.

The etiology of cardiac arrest should actively be pursued immediately after ROSC to identify treatable causes, this includes patient history, 12-lead ECG, laboratory and/or imaging studies [107].

Studies show that cerebral ischemia is associated with poor outcome [108], and that oxygen administration increases cerebral oxygenation [109], hyperoxia could however increase harmful free oxygen radicals [110]. Trials targeting different oxygenation targets are inconclusive [111-115], leading to the recommendation of arterial oxygen saturation should be kept normal, SpO2 94-98% [107].

Hypercapnia rises intracranial pressure by an increase in cerebral blood flow. Contrary, hypocapnia cause cerebral vasoconstriction, potentially inducing cerebral ischemia. Mildly elevated levels of carbon dioxide have been associated with higher cerebral oxygenation [116,117], and in one study, lower biomarkers of cerebral injury

[117]. Results from observational studies are mixed [37,118-121]. The current recommendation is to ventilate patients using lung protective ventilation, extrapolated from ARDS studies [122], and to target normocapnia [107]. The effects of targeted mild hypercapnia versus normocapnia investigated in the TAME-trial [123] will be presented in the close future.

Myocardial dysfunction is common after cardiac arrest [47,124,125], and blood pressure is one of the major determinants of cerebral blood flow [126]. Cardiac arrest is associated with a right shift in cerebral autoregulation [127,128], optimal mean arterial pressure (MAP), in observational studies, has been estimated to be between 85-100 mmHg depending on autoregulatory status, indicating risk of hypoperfusion and cerebral ischemia with hypotension [127,129]. In observational studies hypotension after cardiac arrest is associated with worse outcome [130-137], however, two small pilot trials targeting different levels of blood pressure did not show any benefit in surrogate markers of cerebral injury or survival with a higher blood pressure [113,138]. Guidelines recommend targeting MAP to achieve normal urine output and normal/decreasing lactate, while avoiding hypotension, defined as mean arterial > 65 mmHg [139]. Noradrenaline and dobutamine are the preferred vasopressor/inotropic agents based on safety data [113,138,140].

Coronary reperfusion

The sensitivity for a coronary occlusion with ST-elevation or a new onset left bundle branch block (LBBB) in resuscitated OHCA patients is about 80% [141]. Observational data show increased survival with emergent coronary reperfusion in these patients [142]. Survivors of cardiac arrest, however, have not been shown to have a survival benefit from acute compared to delayed coronary angiography with subsequent reperfusion if appropriate [51,52]. This aggregated evidence has led to the recommendation of performing emergent coronary angiography with subsequent reperfusion in OHCA patients with ST-elevation or new onset LBBB and in patients without ST-elevation/LBBB but with high suspicion of coronary occlusion [139].

Temperature management

After successful mitigation of cerebral injury in dogs with the use of induced hypothermia after cardiac arrest [143], in 2002, two small trials reported improved outcome in OHCA patients resuscitated from ventricular tachycardia/fibrillation after application of induced hypothermia to 32-34ºC for 12-24 hours [144,145] compared to standard care. Subsequently induced hypothermia was implemented clinically, but methodological concerns regarding the supporting evidence were raised. In a large, trial 2013, temperature control at 33ºC did not confer a benefit on outcome compared to 36ºC in OHCA [146], neither did temperature control at 33ºC for 48 hours compared to 24-hours [147], or 31ºC compared to 33ºC [148], or 33ºC versus normothermia (defined as a core body temperature of below 37.8ºC) [41]. In the Hyperion trial, a mixed cohort of IHCA/OHCA patients with initial non-shockable

rhythm had a small beneficial effect on favorable neurological outcome with temperature control at 33ºC compared to 36ºC [149]. This effect was not reproduced in the subgroup analysis of the TTM-2 trial [41]. No support for improved outcome with induced hypothermia has been found in two recent meta-analyses [150,151]. The ESICM-ERC recommendation is to avoid fever up to 72 hours in unconscious survivors of cardiac arrest, but evidence is graded at low certainty [152].

Prognostication

The cause of death after cardiac arrest in about 70% of cases is due to hypoxic-ischemic encephalopathy [44,45]. Only a minority of these patients develop brain death due to brain herniation [153], while most expire after withdrawal of life supporting therapy (WLST) based on a perceived poor probability of neurologic recovery [46]. Ideally WLST should be based on a test with 100 % specificity to predict poor neurological recovery, however, such a test has not yet been discovered. To circumnavigate this issue, neurological prognostication is based on a multimodal approach, using tests with an upper boundary of the 95 % confidence interval for false positive rates below 5 %. At present the multimodal approach include clinical findings, biomarkers, neurophysiology, and imaging techniques (Figure 3) [139].

In absence of confounders, the 2021 ESICM-ERC neurologic-prognostication algorithm suggests poor neurologic recovery in unconscious patients with stereotype flexion in response to pain at 72 hours post arrest with □ 2 positive predictors, defined as: 1) No pupillary and corneal reflexes; 2) Bilaterally absent N20 somatosensory evoked potentials; 3) Highly malignant electroencephalogram; 4) Neuron specific enolase >60 at 48 or 72 hours; 5) Myoclonic status within 72 hours; 6) Extensive, diffuse anoxic injury on computed tomography or magnetic resonance imaging of the brain [139].

A limitation using this approach is that the true prognostic accuracy of most of these tests probably is overestimated, since they have not been evaluated blindly, inducing risk of bias for self-fulfilling prophecy [154,155]. In addition, some predictors of outcome are influenced by confounders commonly encountered in critical care i.e., residual sedation, neuromuscular blockade, sepsis, hypothermia, fever, renal/hepatic failure, hypotension, non-convulsive status epilepticus. Guidelines mandate a washout period of five context sensitive half-lives for the longest acting sedative drug before performing neurologic prognostication, suggesting the use of short acting sedative agents i.e., propofol and remifentanil [139]. Most patients with good neurologic recovery regain consciousness within 3-4 days, with decreasing frequency of good neurological recovery as time to wake up progress [156-158].

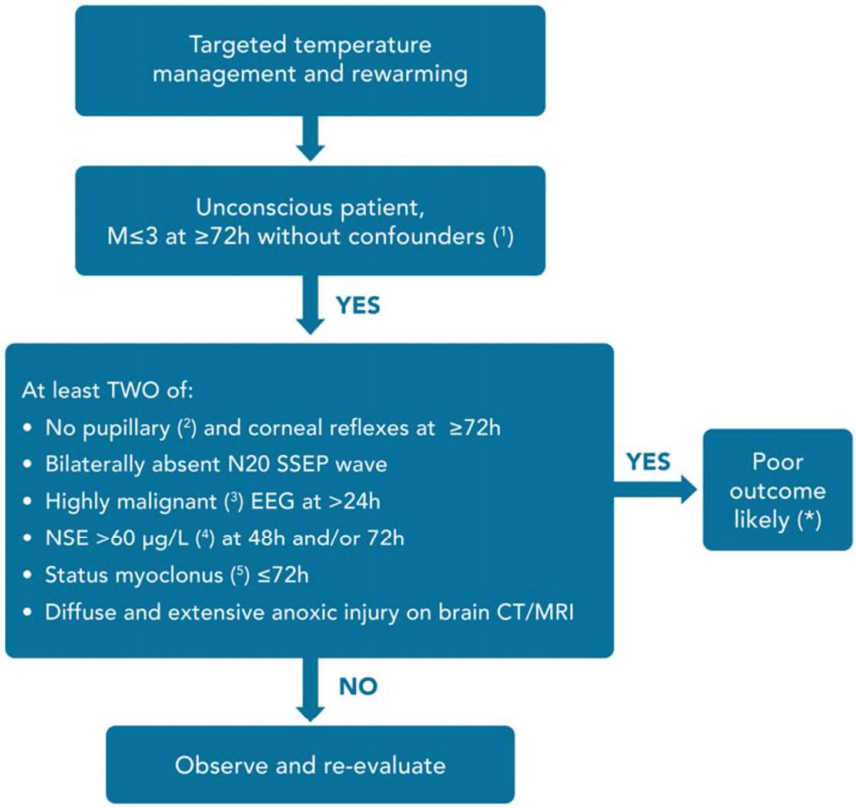

Figure 3
The ESICM-ERC 2021 Neurologic prognostication after cardiac arrest algorithm. EEG electroencephalography; NSE neuron specific enolase; SSEP somatosensory evoked potential; ROSC return of spontaneous circulation. 1) Major confounders may include analgo-sedation, neuromuscular blockade, hypothermia, severe hypotension, hypoglycemia, sepsis, metabolic and respiratory derangements. 2) Use an automated pupillometer, when available to assess pupillary light reflexes. 3) Suppressed background ± periodic discharges or burst suppression, according to American Clinical Neurophysiology Society.4) Increasing NSE levels between 24-48 hours or 24/48 and 72 hours further support a likely poor outcome, 5) Defined as continuous and generalized myoclonus persisting for 30 minutes or more. *) Caution in case of discordant signs indicating a potentially good outcome. © European resuscitation council, reprinted with permission.

In a retrospective validation study, the 2021 ESICM-ERC algorithm has a false positive rate of 0 [95% CI 0-8] %, and sensitivity of 67 [95% CI 59-74] % for detecting poor neurologic recovery, defined as CPC > 2, at 6 months [159].

Circulatory failure

The published incidence of circulatory failure after OHCA varies from 15-68% depending on definition, methodology and studied population [44,149,160]. Reported mortality is about 70% for this subgroup [44,160]. Factors commonly associated with

circulatory failure after cardiac arrest include female sex, age, longer time to ROSC and initial non-shockable rhythm [44,160]. The observed increase in mortality for patients in circulatory failure after cardiac arrest could stem from increased risk of circulatory or multiorgan death, but hypoperfusion could also augment neurologic injuries leading to neurologic cause of death. Observational data suggests better outcome with higher blood pressure [130-135,137,161], however, only two relatively small randomized trials have published neutral results on circulatory interventions and outcome after OHCA [113,138].

Circulatory failure, circulatory shock and hemodynamic failure are clinical medical terms used interchangeably to describe a wide array of symptoms linked to impaired cellular oxygen metabolism, in the setting end-organ hypoperfusion [162]. Circulatory failure infers that the cellular dysoxia [163], metabolism limited by oxygen delivery, is caused by inadequate cardiac output and/or vascular resistance (Figure 4). Due to difficulties in assessing these components clinically, no uniform definition exists. In absence of a strict definition, clinical markers of end-organ tissue hypoperfusion are used as surrogate markers of circulatory failure. These include biomarkers, hemodynamic and clinical findings.

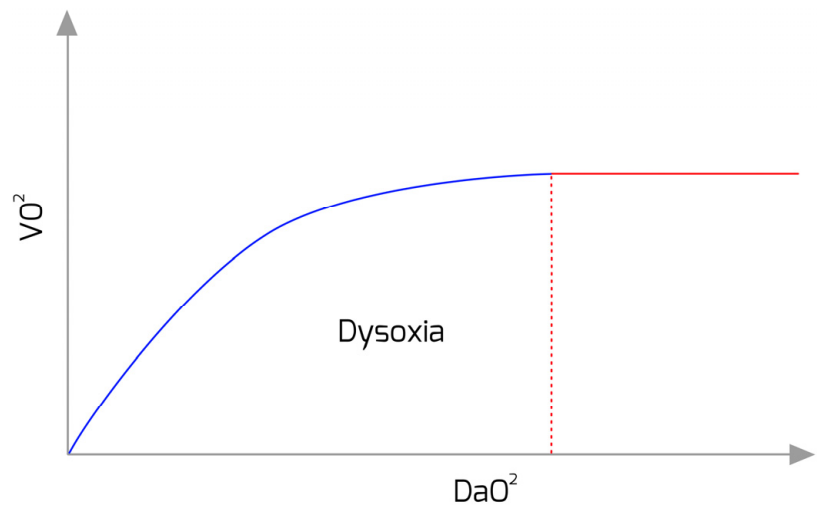

Figure 4
Dysoxia, In the setting of tissue hypoperfusion, cellular metabolism (VO2) is limited by the reduced delivery of arterial oxygen (DaO2).

Hemodynamic and clinical signs associated with circulatory failure

Arterial hypotension is frequently used to define circulatory failure. Cut-offs commonly used to define hypotension vary: 1) Systolic arterial blood pressure < 90 mmHg; 2) Mean arterial pressure (MAP) < 65 mmHg; 3) MAP < 70 mmHg. The rationale for these cut-offs is largely empiric or based on expert opinion [107,162,164].

The widely adopted sequential organ failure assessment (SOFA) score, originally developed as a sepsis severity score [164] contains a cardiovascular component employed in research to grade circulatory failure. Circulatory failure is classified in four ordinal categories from 0 (no circulatory failure) to 4 (severe circulatory failure), based on MAP and inotropic/vasopressor support. The justification for this classification is an increase in mortality with higher cardiovascular SOFA score. The extended cardiovascular SOFA score system (eCvSOFA) was later developed, based on the cardiovascular SOFA score, adding higher resolution of vasopressor dosing [160].

Cold, mottled extremities, increased capillary refill time and oliguria are clinical signs of hypoperfusion, and sometimes included in the definition of circulatory failure.

Biomarkers associated with circulatory failure

Lactate

Oxidative phosphorylation of energy rich substrates produced in the citric acid cycle, is the major source of adenosine triphosphate (ATP), the universal energy molecule used by human cells. During anaerobic conditions this process will halt, leading to accumulation of pyruvate from glycolysis, not being able to be metabolized in the citric acid cycle. The surplus of pyruvate drives its conversion to lactate by lactate-dehydrogenase [165,166] (Figure 5). Most lactate is cleared under aerobic conditions by oxidation in the mitochondria to yield pyruvate and nicotinamide adenine dinucleotide (NAD^+), and to a lesser degree in the liver, by conversion in the Cori-cycle to glucose or glycogen A minor portion is converted by transamination, primarily to alanine [167]. Lactate can also be utilized by the kidneys and heart as an energy substrate.

Lactate is currently employed in routine care of critically ill patients as an indicator of circulatory failure, due to the close pathophysiologic relationship with hypoperfusion induced anaerobic metabolism. Lactate is associated with outcome in multiple critically ill patient populations e.g., sepsis, trauma, cardiogenic shock, respiratory failure and cardiac arrest [168,169]. Lactate levels and kinetics are currently employed in the surviving sepsis guidelines as a marker of severity and to guide resuscitation [170].

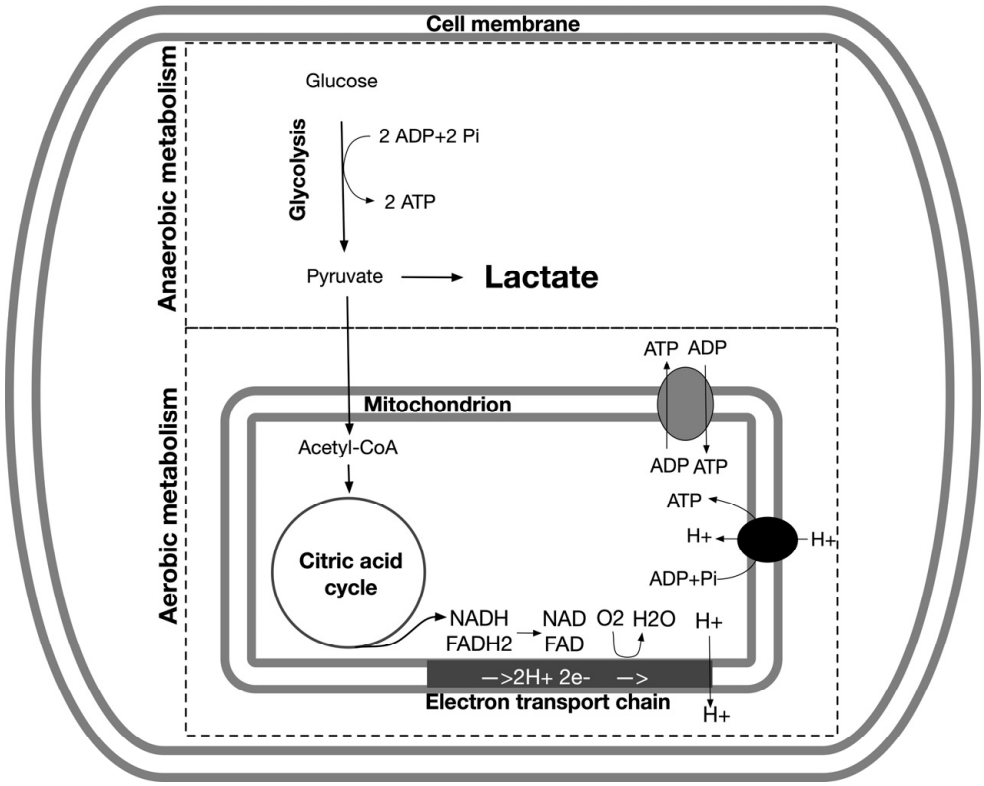

Figure 5
Simplified schematic illustration of cellular metabolism during aerobic and anaerobic conditions

Using lactate for diagnosing circulatory failure can be confounded by other causes of hyperlactatemia, including interference with oxidative phosphorylation (E.g. metformin intoxication, cyanide poisoning), impaired pyruvate dehydrogenase function (E.g. thiamine deficiency), accelerated glycolysis (E.g. B_2-stimulants) or due to decreased lactate clearance (liver and/or renal dysfunction) [165,171].

Copeptin

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), is a peptide hormone released from the posterior pituitary gland that increases solute-free water reabsorption in the renal tubules and systemic vascular resistance by constricting selected arterioles. Elevated AVP levels have been shown to correlate with circulatory failure [172-175]. Measurement of AVP, however, is challenging because of its short half-life, but it can be substituted by measurement of copeptin (also known as CT-proAVP), the C-terminal proteolytic product of the pre-pro-hormone of AVP (Figure 6). Copeptin has been shown to be a reliable surrogate biomarker of vasopressin [176], and levels are significantly increased at hospital

admission in patients with acute coronary syndrome [177]. Also, high copeptin levels are associated with risk of death in patients with cardiovascular failure [178,179], while low levels have been implemented in clinical practice to rule out non-ST-segment acute myocardial infarction [177,180]. Furthermore, copeptin has been suggested as a promising prognostic biomarker after OHCA [181-184].

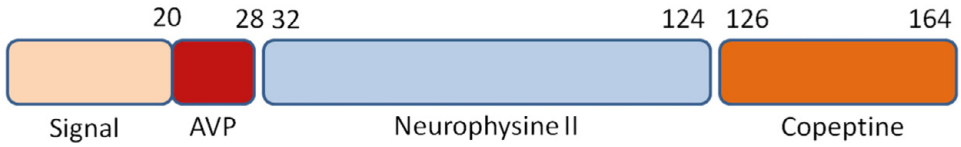

Figure 6
Schematic structure of the 164 amino acid long polypeptide pre-pro-vasopressin precursor, the molecule from which copeptin is released. Illustration by Cyrillec, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=29987414. Reprinted with permission

Aims of this thesis

The aim of this thesis is to investigate the association of early markers of circulatory failure and outcome in the setting of out-of-hospital cardiac arrest:

I. The association between lactate and survival after out-of-hospital cardiac arrest

II. The association between copeptin and survival after out-of-hospital cardiac arrest

III. The influence of circulatory shock after out-of-hospital cardiac arrest on neurologic outcome.

IV. The interaction between early circulatory failure and targeted temperature management at 33ºC on survival after OHCA.

Methods

Table 1

Paper	I	II	III	IV
Design	*Post hoc* analysis of an international, multicenter investigator-initiated, open-label, superiority trial.		Retrospective study of an international post cardiac arrest registry.	*Post hoc* analysis of an international, multicenter, investigator-initiated, open-label superiority trial.
Study population	Unconscious adult survivors of out-of-hospital cardiac arrest of presumed cardiac cause randomized to targeted temperature management at 33ºC versus 36ºC. 2010-2013. n=939.		Unconscious adult survivors after out-of-hospital cardiac arrest included in the INTCAR I or INTCAR II registry. 2006-2017	Unconscious adult survivors of out-of-hospital cardiac arrest of presumed cardiac cause randomized to targeted temperature management at 33ºC versus normothermia. 2017-2020.
	Patients with documented lactate on admission.	Patients included at site participating in the TTM biobank sub-study alive at 24 h.		
Participants	n=877	n=690	n=4004	n=1861

Overview of the methodology used in original publications for this thesis

The TTM-1 trial

The *Targeted temperature management at 33°C versus 36°C after out-of-hospital cardiac arrest, a randomized, parallel groups, assessor blinded clinical trial* (TTM-1 trial) [146], is an investigator initiated, open-label, international, multicenter, superiority trial that investigated outcome after out-of-hospital cardiac arrest with targeted temperature management at 33ºC versus 36ºC. Rationale, design and statistical analysis plan for the TTM-1 trial have been published separately [185,186].

Patients

Adult, (age □18), unconscious (Glasgow Coma Scale < 8) survivors of OHCA with sustained ROSC, (>20 minutes with signs of circulation without the need for mechanical compressions) were eligible for the TTM-1 trial. Major exclusion criteria included: Unwitnessed asystole as primary rhythm, presumed non cardiac cause of arrest, time from ROSC to screening > 240 minutes and systolic blood pressure < 80 mmHg in spite of fluid loading, vasopressor/inotropes or mechanical circulatory support.

Ethics

The trial protocol was approved by ethical committees in each participating country, and informed consent was waived or obtained from all participants or relatives according to national legislation, and in line with the Helsinki declaration [2]. The trial underwent one prespecified interim analysis by the data safety monitoring board and was monitored according to good clinical practice (GCP).

Protocol

After randomization the assigned temperature target was achieved as fast as possible according to local protocols, using any combination of cold intravenous fluids, icepacks, surface- or intravenous temperature control devices. Targeted temperature was maintained until 28 hours after randomization, after which, body temperature was increased by 0.5ºC until a body temperature of 37ºC was reached. Mandatory sedation was tapered or stopped at 36 hours. Body temperature was maintained below 37.5ºC until 72 hours for unconscious patients (Figure 7).

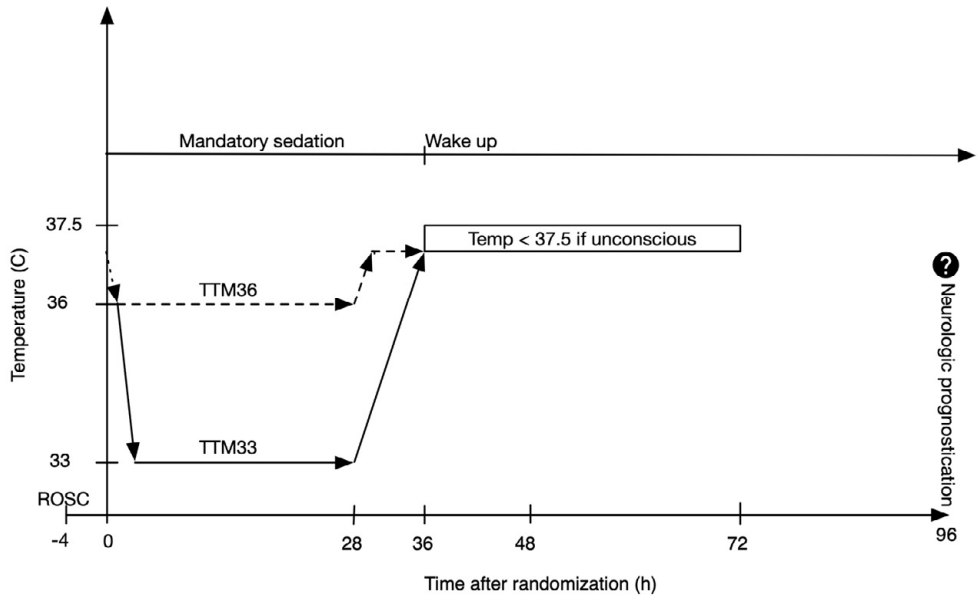

Figure 7
Schematic illustration of the TTM-1 protocol. Unconscious, defined as not following verbal commands; TTM36, Targeted temperature management at 36ºC; TTM33, Targeted temperature management at 33ºC; ROSC, Return of spontaneous circulation.

Hemodynamic monitoring and interventions were according to standard of care at participating site.

Assumptions of a poor neurological function were not allowed to be the reason for withdrawal of active treatment prior to neurological prognostication by a physician blinded to the intervention, at the earliest 108 h after randomization. After the recommendation for continuing or withdrawing life sustaining therapies, based on a prespecified protocol, clinical decision was at the discretion of the health care team

29 out of 36 sites participating in the TTM-1 trial also participated in a biobank sub-study. Blood serum samples were collected from subjects at 24, 48, 72 hours, processed/aliquoted and frozen at study site for storage by the Integrated Biobank of Luxemburg. This process allowed for centralized batch analyses of relevant biomarkers at a later stage.

Outcome

The primary outcome in the TTM-1 trial was survival until end of trial. Secondary outcomes included neurologic outcome at 6 months after the cardiac arrest.

Results

Patients, n=950, were recruited 2011-2013. The trial did not confer any survival benefit with hypothermia at a targeted temperature of 33ºC, as compared to a targeted temperature at 36ºC, hazard ratio 1.06 [95% CI 0.89-1.28].

The TTM-2 trial

Targeted Hypothermia versus Targeted Normothermia after Out-of-hospital Cardiac Arrest. A Randomized Clinical Trial (TTM-2 trial) [41] investigated survival after OHCA in patients randomized to normothermia versus a temperature intervention at 33ºC in the setting of an investigator initiated, international, open-label, assessor blinded, parallel-group superiority trial. The rationale, design and statistical analysis plan for the TTM-2 trial was published separately [187,188]

Patients

Adult (≥18 years), unconscious (unable to follow verbal commands) patients 20 minutes after sustained ROSC (signs of circulation without need for mechanical circulatory support) after OHCA of presumed cardiac or unknown cause of arrest were eligible in the TTM-2 trail. Exclusion criteria included unwitnessed asystole as primary rhythm, screening > 180 min after ROSC, or a do not resuscitate (DNR) order.

Ethics

The TTM-2 protocol was approved by the ethics committees in participating countries. Written informed consent was waived, deferred, or obtained from legal proxies, depending on conditions. Informed consent was acquired from patients regaining mental capacity. The trial underwent two prespecified blinded interim analysis by an independent data and safety monitoring board and was monitored according to GCP.

Protocol

Patients randomized to hypothermia was immediately cooled to targeted temperature management at 33ºC, using surface- or intravascular cooling devices. After 28 hours body temperature was increased by 0.3ºC/hour.

Sedation was mandatory in both intervention groups until 40 hours, after which sedation was tapered or stopped. Patients in both intervention groups, not able to obey verbal commands developing a temperature >37.7ºC before 72 hours after randomization were started TTM at 37.5ºC (Figure 8).

Mandatory neurological prognostication, according to a pre-specified protocol, was performed by a physician blinded to the intervention, for patients remaining in critical care units at 96 hours after randomization. Withdrawal of life sustaining therapies (WLST) due to presumed poor neurologic prognosis was at the discretion of the treating physician after prognostication.

Aside from temperature management and criteria for WLST the TTM-2 protocol did not mandate any specific monitoring or therapy outside standard of care according to international and local guidelines.

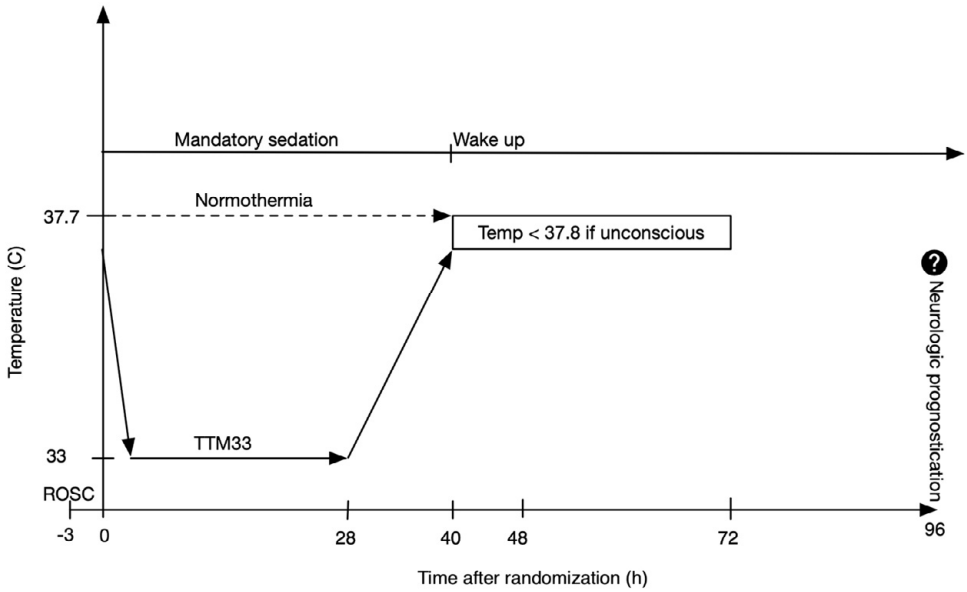

Figure 8
Schematic illustration of the TTM-2 trial protocol. Normothermia, no active temperature control, but treatment of fever only. Fever was defined as a core body temperature of 37.8ºC; Unconscious, defined as patient not able to follow verbal commands; TTM33, Targeted temperature management at 33 ºC.

Outcomes

Primary outcome in the TTM-2 trial was six-month mortality, with secondary outcomes including poor functional outcome, mRS 4-6 [189], at 6 and 24 months.

Results

Patients, n=1900, were recruited 2017-2020. Targeted hypothermia at 33ºC did not decrease incidence of six-month mortality compared to normothermia, relative risk with TTM33, 1.04 [95% CI 0.94-1.14].

The INTCAR registry

The International Cardiac Arrest Registry (INTCAR), is a multinational registry of post-resuscitation cardiac arrest care with the purpose of supporting quality improvement and research. Adult survivors of in/out-of-hospital cardiac arrest admitted to an ICU are consecutively enrolled in the INTCAR registry. The registry contains an Utstein [190] style core dataset and quality metrics for post cardiac arrest

care. Data has been collected both prospectively and retrospectively. All data in the INTCAR registry are de-identified. The major limitations in the INTCAR registry are the lack of a process of validation of the data with source documentation, and no information regarding completeness of screening and inclusion.

Registration in INTCAR stated 2006, and is still ongoing. As of March 2022, the data base contained 7775 individual events, from 47 different centers located in North America and Europe.

Ethics

Centers participate in INTCAR on a voluntary basis, without reimbursement for enrolling patients in the INTCAR registry. All sites have received local ethical review board approval with informed consent either obtained or waived from all participants according to national and local legal requirements, and in line with the Helsinki declaration[191]. Ethical approval for the Swedish participation in the INTCAR registry was obtained from the ethical review board in Lund, reference number: REPN Lund Dnr 2007/272.

Patients

Paper III is based on data from the INTCAR I and II subsets, collected 2006-2017, containing data from 42 centers (45% European) with 5943 individual events of which 4391 were OHCA.

Paper I-II

Papers I and II are briefly presented in this section, for a more detailed presentation please see attached original prints [192,193].

Objective

Paper I-II are *post hoc* analyses from the TTM-1 trial. The general objective in these papers was to explore biomarkers that were considered pathophysiologically related to circulatory failure, and their association with survival after out-of-hospital cardiac arrest.

Paper I

Hypothesis: Lactate levels after OHCA are associated with 30-day mortality.

Paper II

Hypothesis: Copeptin levels are associated with 30-day mortality and circulatory failure in OHCA.

Patients

The TTM-1 trial's intention to treat population, n=939 (I), and a subset of these patients from sites participating in the biobank sub-study alive at 24-hours (II).

Methods

Paper I

Lactate concentration collected at hospital admission and at 12-hours after randomization were used to estimate the independent association with 30-day mortality for: 1) Admission lactate; 2) 12-hour lactate and 3) 12-hour lactate clearance (defined as ((admission lactate - 12-hour lactate)/admission lactate)) and 4) 12-hour lactate clearance in a subgroup of patients with admission lactate > median, 6 mmol/l.

Results are presented as odds ratios (OR), and independent OR in a model adjusted for confounders of death after OHCA. The area under the receiver operator curve (AUROC) was used to evaluate the prognostic properties of for lactate metrics.

Paper II

Blood serum samples from the TTM-1 biobank were batch analyzed for copeptin levels using the Brahms Kryptor Compact Plus system (Thermo Fisher Scientific Brahms, Germany) after the completion of the trial.

As a primary analysis, the independent association between copeptin at 24-hours and 30-day survival was estimated using Cox-regression analysis.

To estimate the association with circulatory failure, the binary cardiovascular deterioration composite (CvDC), was devised. The CvDC was considered positive if the patients eCvSOFA score [160] was □5, or died from circulatory cause within ± 12 h of copeptin sample, or if eCvSOFA score increased more than two points within the previous 24 h.

Secondary analyses included: 1) The independent association of copeptin at 24-hours with incidence of circulatory cause of death censored at 30-days, and 2) The independent association of Copeptin at 24-hours with circulatory failure (positive CvDC).

All models were adjusted for early predictors of death after OHCA, using the predictors of the TTM-Score [194]. Due to missingness in the dataset, analyses were

performed on pooled datasets for the explanatory models based on multiple imputations by chained equations for all predictors and outcomes used in statistical models [195].

Paper III

Paper III is briefly presented in this section, for a more detailed presentation please see attached manuscript.

Objective

In paper III the objective was to investigate the independent association of shock on hospital admission, and the interaction of shock on admission with pre-arrest cardiovascular disease, on the neurologic outcome after OHCA.

Patients

Adult (age ≥18 years), unconscious (unable to follow verbal commands) patients after OHCA included in the INTCAR registry 2006-2017.

Subgroup analysis (76 % of total cohort), consisted of patients with continuous variables linearly associated with neurologic outcome in our model.

Methods

Shock on hospital admission was captured in the INTCAR case record form, and defined as: Systolic blood pressure < 90 mmHg and/or the need for supportive measures, such as inotropes, vasoactive drugs, mechanical circulatory support devices to maintain a systolic blood pressure ≥ 90 mmHg or end-organ hypoperfusion, at the first hospital unit the patient presented at after the OHCA.

Neurologic outcome at hospital discharge was based on the Cerebral Performance Category [196] dichotomized as good (CPC 1-2) or poor (CPC 3-5)

Odds ratios for good neurologic outcome at hospital discharge were assessed using generalized additive methods [197]. The model was adjusted for early prognostic factors and pre-arrest cardiovascular morbidity, and estimated from a pooled dataset based on multiple imputations by chained equations[195] for all predictors and outcomes used in the model.

Paper IV

Paper IV is briefly presented in this section, for a more detailed presentation please see attached manuscript.

Objective

The primary objective for this analysis was to investigate the association of survival with temperature intervention in three different subgroups based on vasopressor support on admission, after out-of-hospital cardiac arrest.

Secondary objectives included estimating the cumulative risk of death categorized as neurologic or non-neurologic with an intervention at 33ºC versus normothermia in the vasopressor support subgroups.

Patients

Patients included in the TTM-2 trial categorized in three groups based on vasopressor support on admission: 1) No vasopressor support (No-VS), mean arterial blood pressure (MAP) □ 70 with no inotropic or vasopressor support; 2) Moderate vasopressor support (Moderate-VS), MAP < 70 or any dose dopamine, or dobutamine, or noradrenaline/adrenaline dose □ 0.25 µg/kg/min; 3) High vasopressor support (High-VS), noradrenaline/adrenaline dose > 0.25 µg/kg/min.

Methods

A priori categorization of vasopressor support groups was based on the lowest vasopressor dose causing separation of 180-day all-cause mortality for three groups (Figure 9).

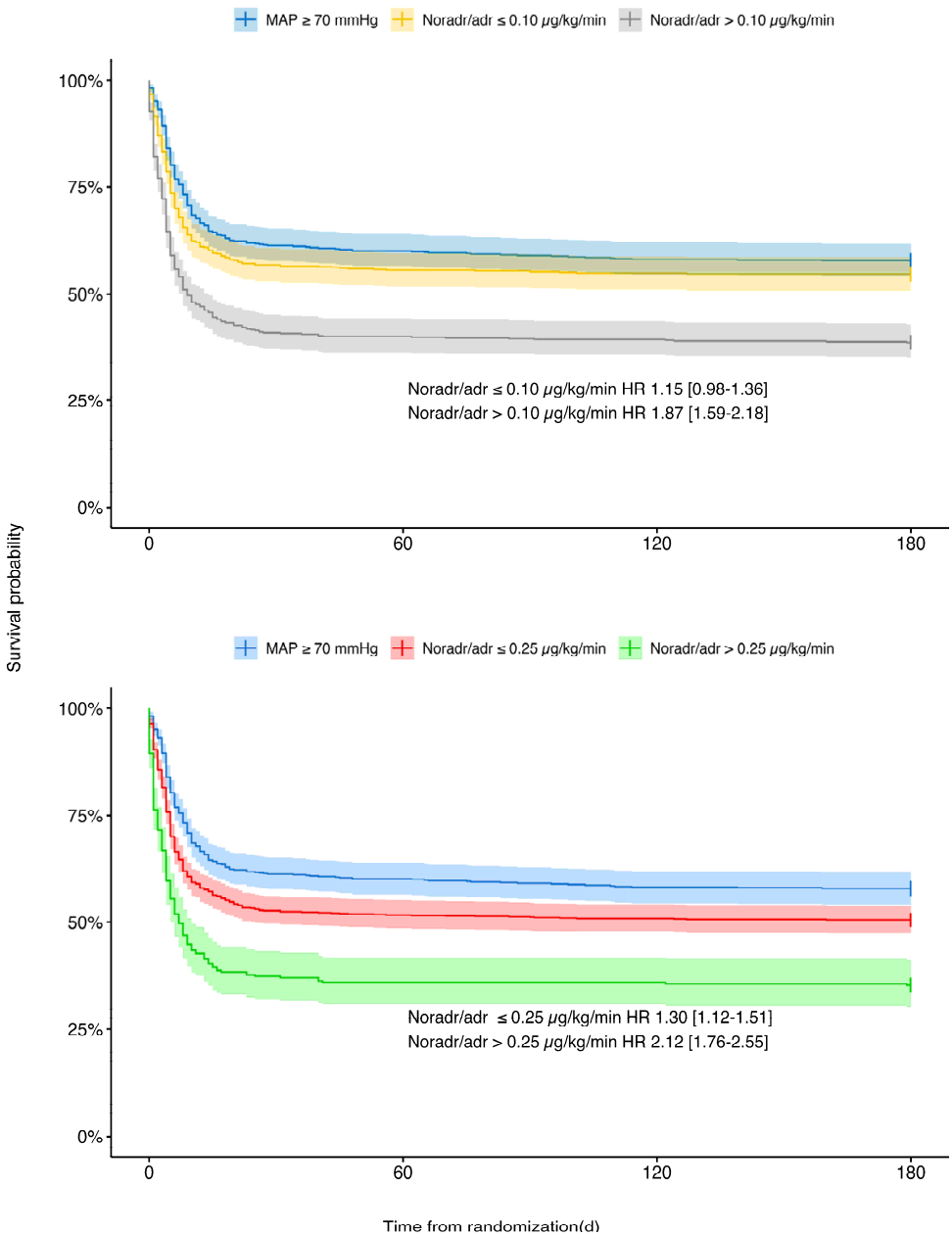

Figure 9
Survival probability after cardiac arrest censored at 180 days for the TTM-2 population stratified according to circulatory status on admission based on all randomized patients. Hazard ratios (HR) are presented with 95% confidence intervals. Mean arterial pressure (MAP) □ 70 mmHg with no vasopressor/inotropes as reference category; HR, Hazard Ratio; Noradr, Noradrenaline; Adr, Adrenaline.

The hazard ratio for all-cause death and cause of death in vasopressor support groups stratified by temperature intervention was estimated by Cox-regression analysis.

A sensitivity analysis was performed estimating the HR for all-cause survival with the combination of TTM33 and different levels of vasopressor support on admission in a model adjusted for known early predictors of survival. Results were based on estimates from a pooled dataset based on multiple imputations by chained equations [195] for all predictors and outcomes used in the model.

Results

Paper I

In the TTM-1 trial, 93% and 87% of all patents had lactate recorded at admission and 12 hours respectively. In a mixed effects model, admission lactate was significantly higher at all measured timepoints until 36 hours in patients dead at 30 days compared to survivors, p<0.001 (Figure 10). Median lactate at admission for survivors was 4.7, with interquartile range [IQR 2.4-8.0] and 7.3 [IQR 4.5 -10.7] mmol/l for patients dead at 30-days.

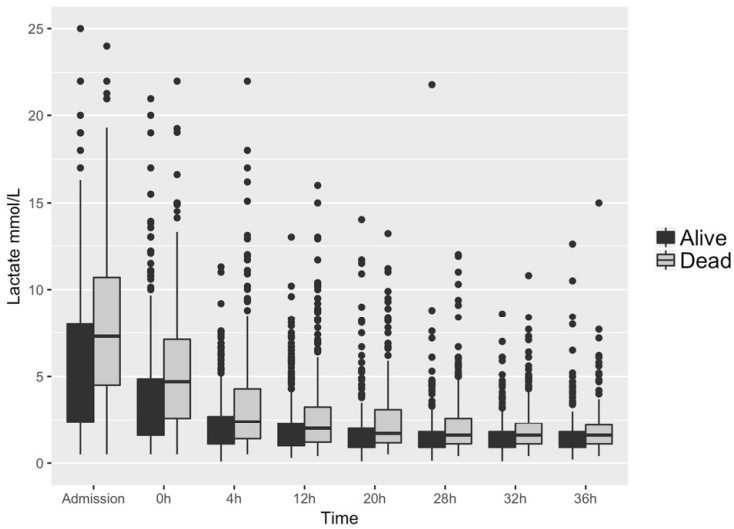

Figure 10
Distribution of lactate over time in survivors of out-of-hospital cardiac arrest. In a mixed model. Patients dead by day 30 had higher average lactate, p<0.001. Düring et al Acta Anestesiol. Scand 2018. Reprinted with permission.

The unadjusted OR for death within 30 days, with every 1 mmol/L increase in admission lactate, was 1.12 [95% CI 1.08-1.16], and at 12 hours 1.21 [95% CI 1.12-1.31]. For 12-hour lactate clearance the OR was 1.003 [95% CI 1.0-1.01] per percentage point increase in 12-hour lactate clearance (Table 2).

After adjusting for confounders of outcome, admission lactate and 12-hour lactate levels remained significant independent predictors of death by day 30 while 12-hour lactate clearance did not (Table 2). In the subgroup analysis of patients with admission lactate above the median, each percentage point increase in 12-hour lactate clearance was associated with improved outcome with an OR of 0.99 [95% CI 0.98-0.99] for risk of death at 30 days, retaining significance after adjusting for confounders.

Table 2

	Unadjusted analysis			Adjusted analysis		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Admission lactate, n=877	1.117	1.078 – 1.159	< 0.001	1.075	1.029 – 1.124	0.001
Lactate at 12 h, n=750	1.206	1.116 – 1.310	< 0.001	1.117	1.015 – 1.234	0.026
Lactate clearance 12 h, n=702	1.003	1.000 – 1.006	0.034	1.001	0.998 – 1.005	0.531

Odds ratios for death by day 30 after out-of-hospital cardiac arrest. Models were adjusted for age, sex, preexisting liver cirrhosis, time to ROSC, shock on admission, S-T elevation myocardial infarction, bystander CPR, witnessed arrest, shockable rhythm, dose of adrenaline, temperature allocation. For 12-hour lactate and 12-hour lactate clearance adjustments were made for lactate at admission. OR, Odds Ratio; CI, confidence interval. Düring et al Acta Anestesiol. Scand 2018. Reprinted with permission.

The prognostic discrimination for short term survival was poor for admission lactate with an AUROC of 0.65 [95% CI 0.61-0.69], and for 12-hour lactate 0.61 [95% CI 0.57-0.65], while non-significant for 12-hour lactate clearance, 0.53[95% CI 0.49-0.57] (Figure 11).

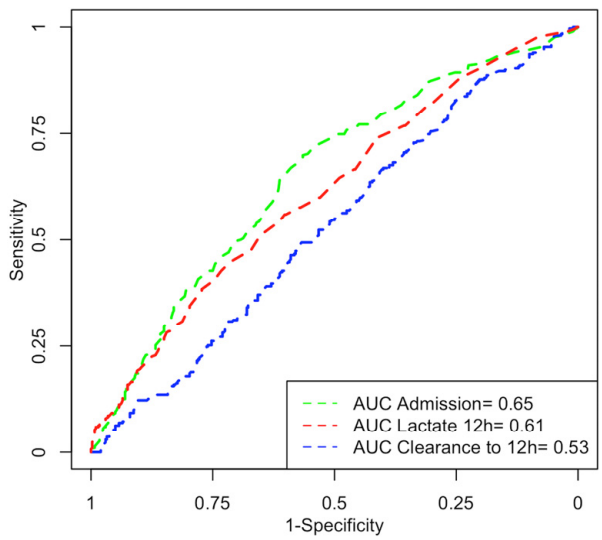

Figure 11
The prognostic precision for lactate as a predictor for 30-day mortality in survivors of out-of-hospital cardiac arrest. The area under the curves (AUROCs) in the receiver operator characteristics curves depict the prognostic performance of admission lactate, 12-hour lactate, and 12-hour lactate clearance, respectively. Düring et al Acta Anestesiol. Scand 2018. Reprinted with permission.

Paper II

Of the 690 patients included in the sub study population 39.6% died within 30 days. Copeptin levels were significantly lower in survivors than in patients dead by day 30, with largest difference observed at 24-hours, 17.2 [IQR 9.9-36.2] vs 51.1 [IQR 19.6-99.5] pmol/l, p<0.001 (figure 12)

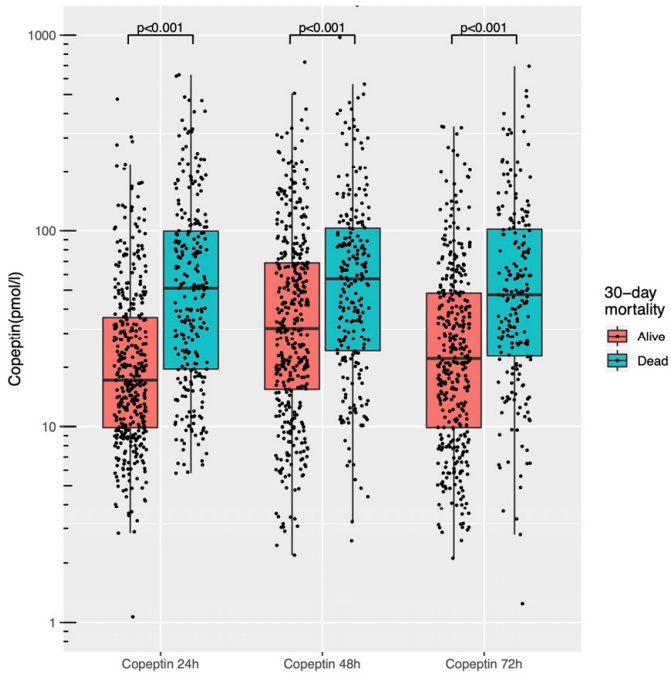

Figure 12
Copeptin levels stratified according to 30-day mortality. Box plot illustrating difference in copeptin levels measured at 24, 48, and 72 h after cardiac arrest in survivors vs. non-survivors at day 30. Copeptin on Y-axis is on a log scale.

The incidence of death was independently associated with log2-transformed copeptin, hazard ratio (HR) 1.17 [95% CI 1.06– 1.28] (Figure 13); for samples at 24 h, significance was lost at 48, and 72-hours. Incidence of crude 30-day mortality was significantly higher in patients with copeptin levels above, compared to those below, median at 24-hours $p<0.001$ (figure 14)

Copeptin was independently associated with a circulatory cause of death within 30-days, OR 1.03 [1.01–1.04] for log2 transformed copeptin at 24 hours (Figure 15), while not significant at 48 and 72 hours.

Copeptin at 24, 48 and 72 hours were independently associated with cardiovascular deterioration, as estimated by a positive cardiovascular deterioration composite, with the highest OR at 24 hours for log2 transformed copeptin, 1.05 [1.02–1.08] (Figure 16).

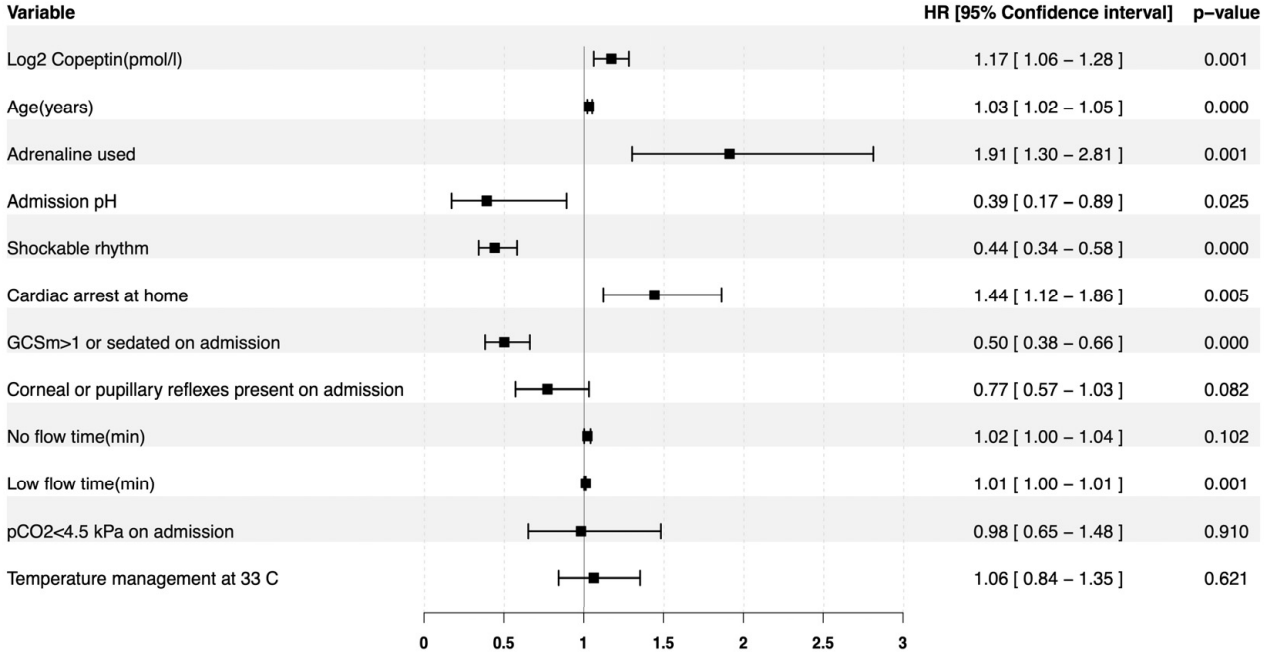

Figure 13
Forest plot displaying hazard ratio for death within 30 days in a multivariate Cox proportional hazards adjusted for Copeptin at 24 hours. No flow time, time from cardiac arrest until start of chest compression or return of spontaneous circulation, whichever comes first; low flow time, from start of chest compressions until return of spontaneous circulation.

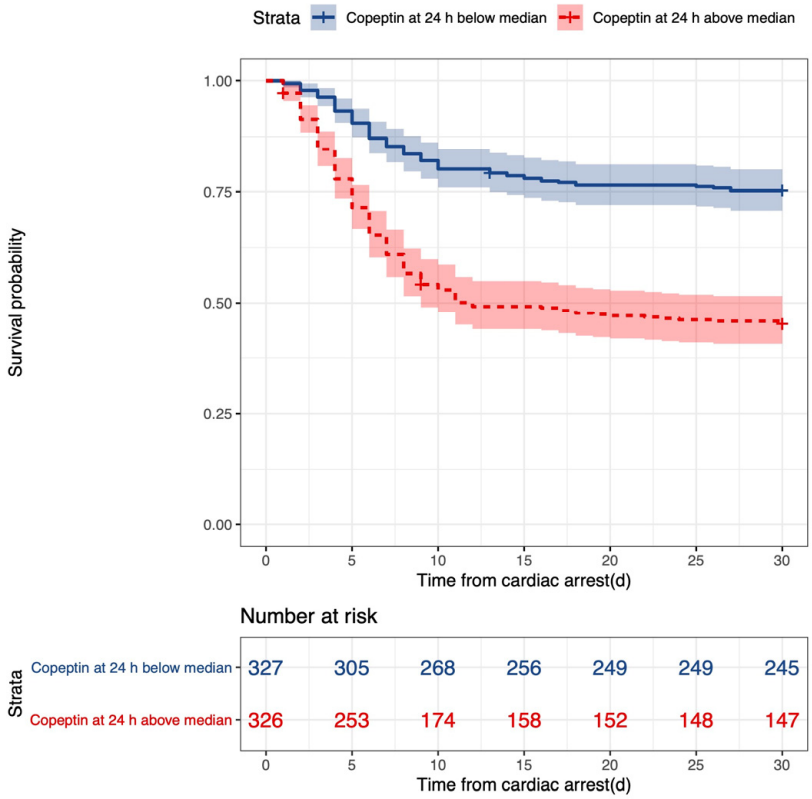

Figure 14
Probability of 30-day survival. Kaplan-Meier graph illustrating the probability of survival after cardiac arrest according to copeptin levels stratified as above or below median at 24 h. Outcome was censored after 30 days. Shaded areas indicate 95% confidence interval. Survival was significantly higher in the group with copeptin levels below median at 24 h, $p < 0.001$

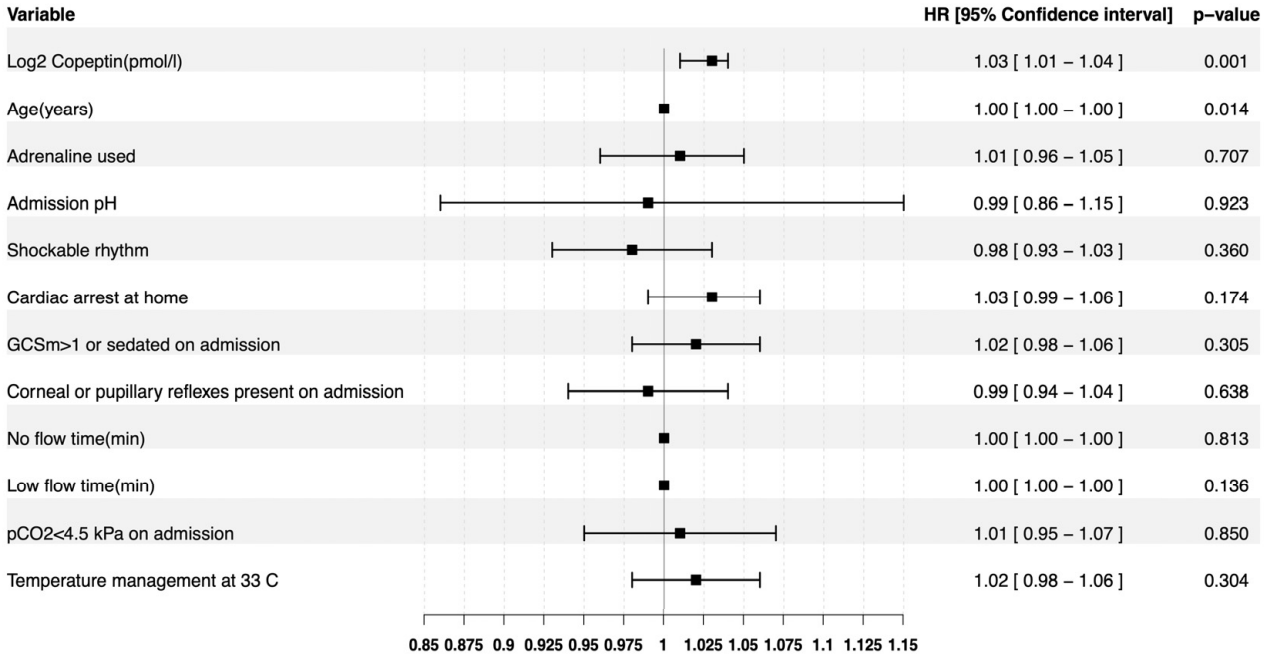

Figure 15
Forest plot displaying odds ratios for circulatory cause of death within 30 days of cardiac arrest in a multivariate logistic regression model adjusted for copeptin at 24 hours. No flowtime, time from cardiac arrest until start of chest compression or return of spontaneous circulation, whichever comes first; low flow time, from start of chest compressions until return of spontaneous circulation.

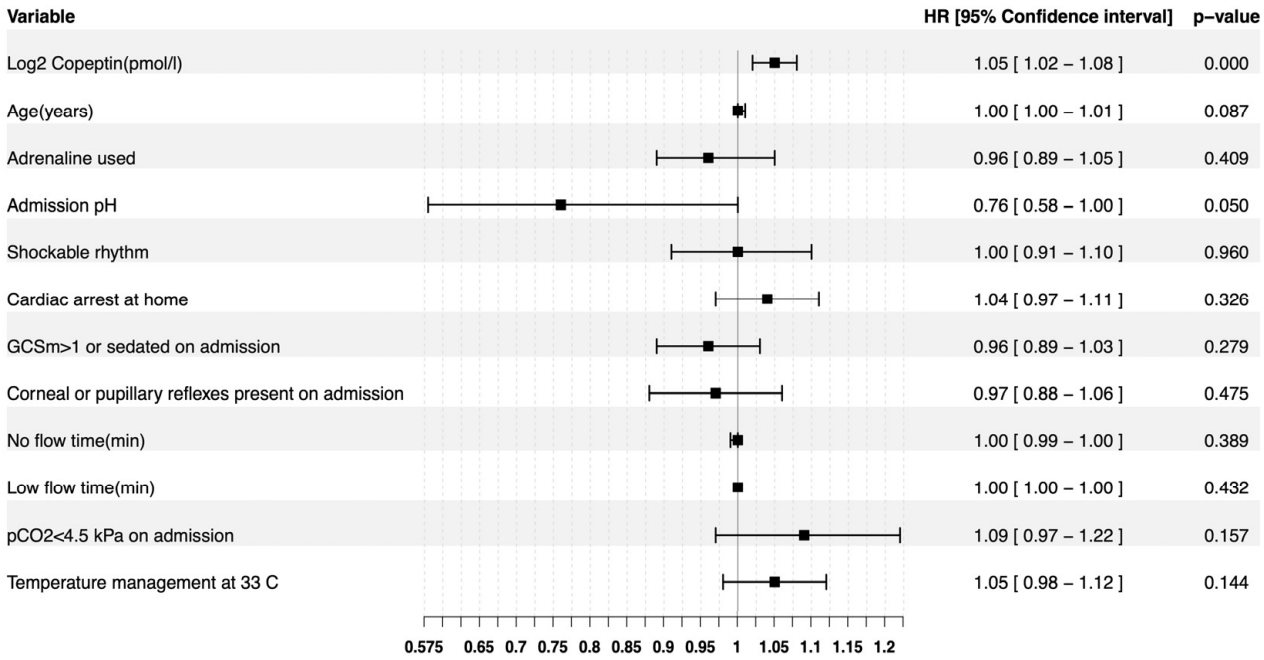

Figure 16
Forest plot displaying odds ratios for a positive cardiovascular deterioration composite (CvDC) 12-36 hours after randomization, in a multivariate logistic regression model adjusted for copeptin at 24 hours. CvDC was considered positive if the patient had an extended cardiovascular SOFA score □5 at 24 hours, or died from circulatory cause between 12-36 hours. No flow time, time from cardiac arrest until start of chest compression or return of spontaneous circulation, whichever comes first; Low flow time, from start of chest compressions until return of spontaneous circulation.

Paper III

Out of the 4004 (67% of INTCAR population) patients included in analysis, 38% were in circulatory shock on admission. A total of 32 % of all included patients had good neurologic outcome (CPC < 3) at hospital discharge. Circulatory shock on admission was more frequent with female sex, increasing age, unwitnessed arrest, non-shockable rhythm as first documented rhythm, longer time to ROSC and higher burden of co-morbidities.

For the full population, the adjusted OR for circulatory shock at hospital admission as an explanatory factor for good neurologic outcome was 0.60 [95% CI 0.46 - 0.79] (Figure 17)

Continuous variables in our model were linearly associated with neurologic outcome in a subgroup aged 42 - 92 years, with time to ROSC 9 - 87 min, constituting 76% of the total cohort. For these patients the adjusted OR for good outcome with circulatory shock at admission and none of the defined pre-existing comorbidities, was 0.65 [95% CI 0.47 - 0.90].

The OR for the interaction between circulatory shock and pre-existing hypertensive disease, was 0.64 [95% CI 0.42 - 0.98] (Figure 18), indicating 36% worse odds for good outcome in patients with circulatory shock and a history of hypertension compared to circulatory shock without previous hypertension. Contrary, in circulatory shock and pre-existing arrhythmia the OR for the interaction was 1.96 [1.03 - 3.71], indicating roughly double the odds for good outcome compared to circulatory shock alone.

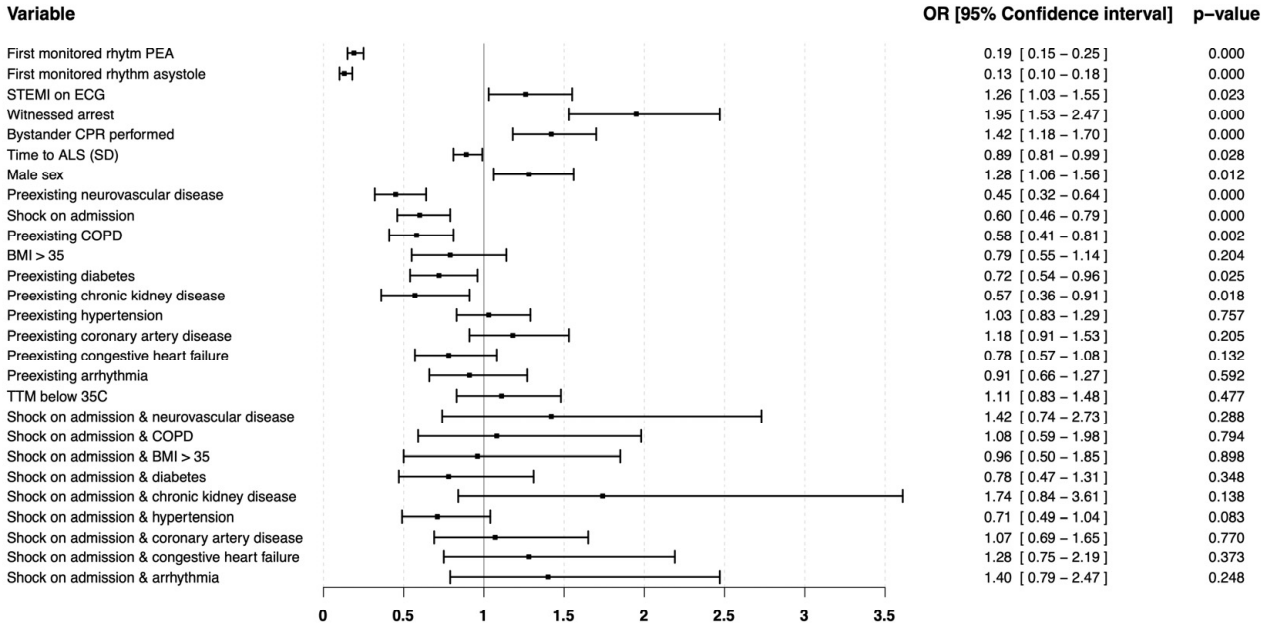

Figure 17
Forest plot illustrating the odds ratios for Cerebral Performance Category 1-2, in a multivariate generalized additive methods model. Analysis was performed in the full cohort, n = 4004. The reference category for first monitored rhythm is shockable rhythm (Ventricular fibrillation or ventricular tachycardia). Time to ALS time has been square root transformed, scaled to standard deviations and centered. Model is adjusted for time to return of spontaneous circulation and age but variables are not presented due to nonlinearity. PEA; Pulseless electrical activity, STEMI; ST-Elevation myocardial infarction, ECG; Electrocardiogram, CPR; Cardiopulmonary resuscitation, SD; Standard deviation, COPD; Chronic pulmonary obstructive disease, BMI; Body mass index, TTM; Targeted temperature management.

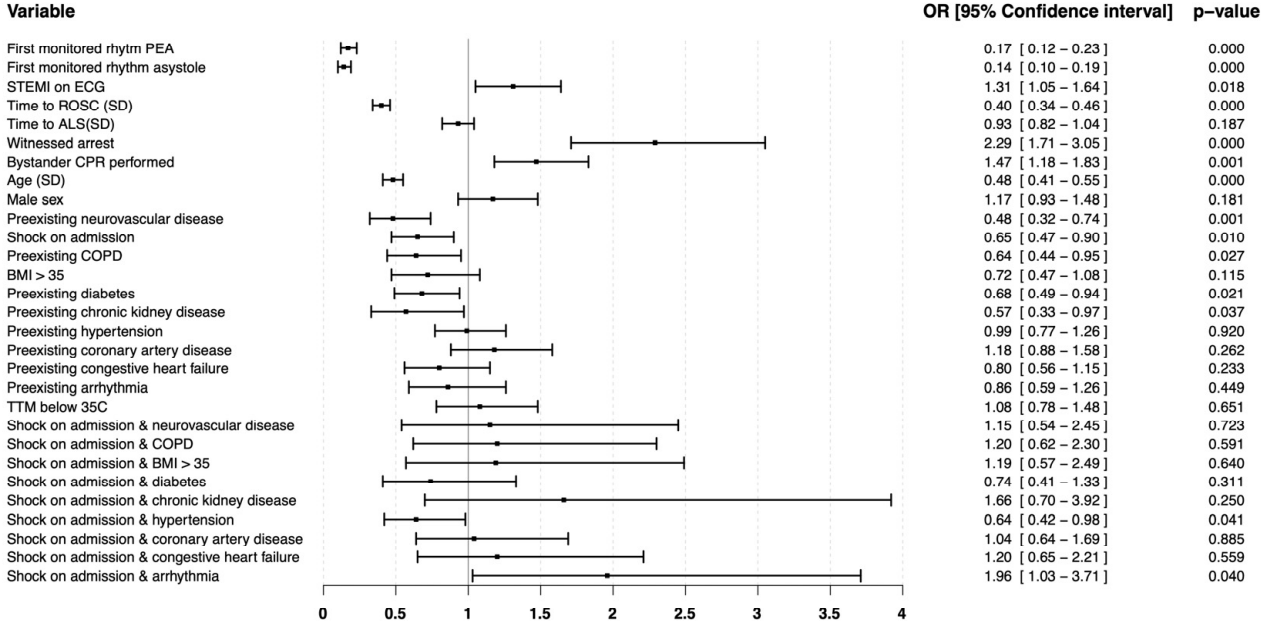

Figure 18
Forest plot illustrating the odds ratios for Cerebral Performance Category 1-2, in a multivariate generalized additive methods model. Analysis was performed in a subgroup of patients with linear continuous explanatory variables, aged 42 - 92 years, with time to ROSC 9 - 87 minutes. The reference category for first monitored rhythm is shockable rhythm (Ventricular fibrillation or ventricular tachycardia). Age (years) and time to ROSC (minutes) have been transformed to normality by ordered quantiles, time to ALS has been square root transformed. After transformation, the variables have been scaled to standard deviations and centered. PEA; Pulseless electrical activity, STEMI; ST-Elevation myocardial infarction, ECG; Electrocardiogram, ROSC; Return of spontaneous circulation, CPR; Cardiopulmonary resuscitation, SD; Standard deviation, COPD; Chronic pulmonary obstructive disease, BMI; Body mass index, TTM; Targeted temperature management.

Paper IV

Out of the 1861 patients included in the TTM-2 intention to treat population, 36%, 48%, and 16% had No-VS, Moderate-VS and High-VS respectively. The incidence of death was higher with vasopressor support on admission, HR 1.30 [95% CI 1.12-1.51] for Moderate-VS, and High-VS HR 2.12 [95% CI 1.76-2.55] compared to No-VS. When stratifying patients according to temperature intervention, the incidence of death at 180 days was higher with a temperature intervention at 33ºC compared to normothermia in the Moderate-VS group, HR 1.22 [95% CI 1.01-1.47], no significant interaction between intervention and vasopressor support on admission was detected in No-VS and High-VS groups (Figure 19).

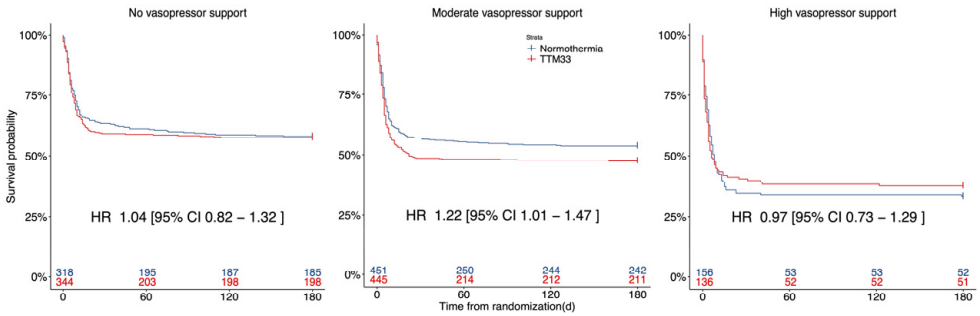

Figure 19
Kaplan-Meier graph censored at 180 days indicating probability of survival in subgroups of vasopressor support on admission, stratified according to temperature intervention. No vasopressor support, mean arterial blood pressure (MAP) □70 with no inotropic or vasopressor support; Moderate vasopressor support, MAP < 70 or any dose dopamine, or dobutamine, or noradrenaline/adrenaline dose □0.25 µg/kg/min; High vasopressor support, noradrenaline/adrenaline dose > 0.25 µg/kg/min. Colored numbers at bottom of plot illustrates number of patients at risk in respective strata at specified timepoint. The vertical tick-marks correspond to censored data. Hazard ratios (HR) are presented with 95% confidence intervals (CI); TTM33, Targeted Temperature management at 33ºC.

Cause of death within 30 days after randomization, dichotomized as neurologic or non-neurologic, was available for 96% of the study population. The Moderate-VS group had an increased incidence of non-neurologic death, HR 1.61 [95% CI 1.21-2.16]. The interaction of vasopressor support on admission with temperature intervention was not associated with cause of death in No-VS and High-VS groups (Figure 20).

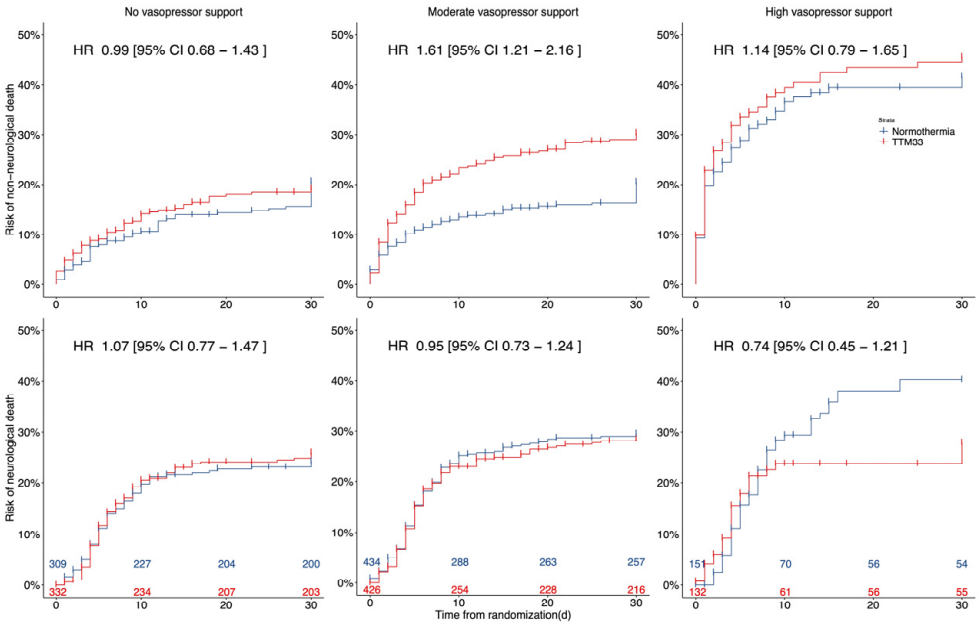

Figure 20
Kaplan-Meier graph censored at 30 days indicating cumulative risk of non-neurological and neurological mortality in subgroups of vasopressor support on admission, stratified according to temperature intervention. No vasopressor support, mean arterial blood pressure (MAP) □ 70 with no inotropic or vasopressor support; Moderate vasopressor support, MAP < 70 or any dose dopamine, or dobutamine, or noradrenaline/adrenaline dose □ 0.25 µg/kg/min; High vasopressor support, noradrenaline/adrenaline dose > 0.25 µg/kg/min. Colored numbers at bottom of plot illustrates number of patients at risk in respective strata at specified timepoint. The vertical tick-marks correspond to censored data. Hazard ratios (HR) are presented with 95% confidence intervals (CI); TTM33, Targeted Temperature Management at 33ºC.

TTM33 in patients with Moderate-VS was associated with a lower heart rate at 4-32 hours with a median difference at 28 hours of -15 [99.7% CI -18 to -9] BPM. In these patients MAP was also lower, at 32-64 hours, compared to patients treated at normothermia, peaking at 64 hours with a median difference of -5 [99.7% CI -8 to -1] mmHg at 64 hours (Figure 21). The major difference in hemodynamic response to TTM33 between groups were: 1) No increase in heartrate for patients with vasopressor support after rewarming; 2) No decrease in blood pressure at rewarming for patients with No-VS. Lactate was minimally increased in all subgroups with an intervention at 33ºC.

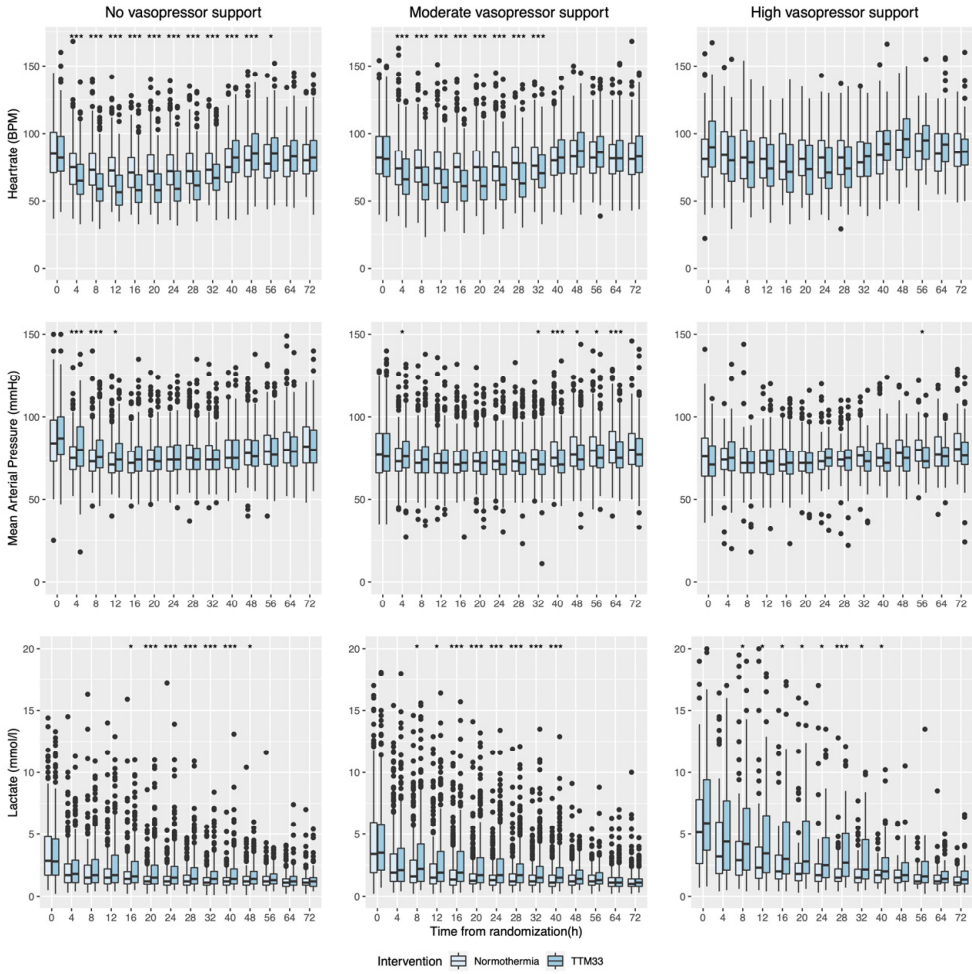

Figure 21:
Heart rate, mean arterial pressure and lactate during the 0-72 h after randomization in groups of different levels of circulatory support on admission and stratified by temperature intervention at 33ºC vs normothermia. No vasopressor support, mean arterial blood pressure (MAP) ≥ 70 with no inotropic or vasopressor support; Moderate vasopressor support, MAP < 70 or any dose dopamine, or dobutamine, or noradrenaline/adrenaline dose ≤ 0.25 µg/kg/min; High vasopressor support, noradrenaline/adrenaline dose > 0.25 µg/kg/min. Boxes represents the interquartile range (IQR), with medians marked as vertical bands. Whiskers symbolize 1.5 x IQR, and dots outside this range represent outliers. TTM33; Targeted Temperature Management at 33ºC. * p<0.003, ** p<0.0001, *** p<0.00001.

Discussion

The incidence of OHCA is reported to be 89/100000 inhabitants per year, and resuscitation is attempted in 50-60% of these events [54]. Only 12 % of patients where resuscitation is started survive [62], making cardiac arrest the third most common cause of death in adults in Europe [54,88]. Most of these patients die from severe neurological injuries [46]. While no specific therapy has proven effective for either survival or neurologic recovery, survival rates have doubled over the last 20 years [198]. Much of this progress could be attributed to more frequent and shorter time to CPR [198] including increased rate of bystander CPR, stating the obvious - tissue perfusion does matter.

At present, the effect of improved hemodynamic control to mitigate secondary brain injury remains to be studied in clinical trials. Hemodynamic interventions can paradoxically infer increased risk of cardiovascular adverse effects [199-202], why individually titrated hemodynamic goals could be one strategy in advancing results of post cardiac arrest care. Prerequisites for this approach is a robust definition of circulatory failure based on individual characteristics rather than a static "one size fits all" definition. A combination of early bio- and hemodynamic markers alone or in combination with patient baseline characteristics could be one strategy to stratify optimal hemodynamic support in the context of OHCA.

In this thesis we found that early bio- and hemodynamic surrogate markers of circulatory failure are independently associated with outcome after OHCA. In addition, we describe the association of vasopressor support on admission in combination with TTM33 on outcome after OHCA.

Lactate (Paper I)

Lactate levels at admission and 12-hours were independent markers of 30-day survival.

Measurement of lactate and lactate kinetics are established as methods for estimating illness severity in multiple fields, including trauma [203-205] and sepsis [168,206], although the level of evidence is low [170]. Previously, lactate have been associated with outcome after cardiac arrest [207-215]. Most of this evidence is based on registries or smaller retrospective studies. Our study adds to the level of evidence

by introducing results from a large population with prespecified outcome and sampling.

Lactate sampled at admission and 12-hours in our study was strongly associated with 30-day survival. Given the close association with anaerobic metabolism it is reasonable to assume lactate corresponds to intra-arrest tissue hypoperfusion and indirectly outcome, however, the predictive precision of these measures was poor as estimated by their respective AUROC. The accuracy for lactate to predict survival is in the same range in sepsis [216,217] and cardiac arrest [218].

Since lactate is usually cleared to normal physiologic levels within a six hour period [168] with restored normal hemodynamic function it is reasonable to suppose that sampling at different times may represent different pathophysiologic mechanisms. 12-hour lactate may represent circulatory status post arrest, as opposed to admission lactate representing pre- and intra-arrest pathophysiology. Assuming outcome is mostly dependent on cerebral hypoperfusion intra-arrest, this may explain the poor predictive precision for 12-hour lactate. In addition multiple possible confounders could have influenced the results: 1) Lactate levels at admission could also be associated with the cause of arrest; 2) Accelerated glycolysis due to adrenaline delivered intra-arrest [219]; 3) Poor lactate clearance due to pre-arrest liver disease or intra-arrest liver hypoperfusion; 4) Seizures; 5) Hyperglycemia; 6) Thiamine deficiency.

The unadjusted OR for 12-hour lactate clearance was significantly increased with increasing clearance in our analysis. This is counterintuitive to what one might expect and in contrast to previous studies [207,208,220-222]. We believe this may reflect that if enough time is allowed to pass, clearance will be lower in patients with normal or slightly elevated admission lactate, and thus higher probability of survival. After adjusting for possible confounders lactate clearance no longer remained significant. Increased 12-hour lactate clearance was, however, a significant predictor of survival in patients with admission lactate above > 6 mmol/l, retaining significance in adjusted analysis.

Copeptin (Paper II)

Copeptin was found to be a time sensitive, independent marker of 30-day survival, cardiovascular failure and circulatory cause of death after out-of-hospital cardiac arrest.

We hypothesized that copeptin release as a surrogate measure of vascular tone is associated with circulatory failure, short term mortality and cause of mortality after OHCA. Our findings regarding short time survival are consistent with those of previous smaller studies in cardiac arrest populations [181-184]. After adjusting for early predictors of death in OHCA only copeptin sampled at 24 hours remained significant. Assuming that most of the burden of mortality in this population is

caused by cerebral injuries, sustained peri-arrest, samples collected at 24-hours or later might not reflect this pathology since copeptin is rapidly cleared from the circulation [223]. This could have confounded our results and explain the lower effects estimate as compared to some of the previous studies [181,182,184]. Copeptin was shown to be associated with temperature change, rather than absolute temperature. Thus, it is also possible that 48- and 72-hour samples of copeptin were influenced by normalization of temperature in the TTM33 intervention group at 28 hours, confounding the results.

The independent association of copeptin at 24-hours with circulatory death within 30-days was statistically strong, but clinically not relevant. Patients suffering circulatory cause of death, do so earlier than those dying from other causes [46]. This could imply that patients dying before 24-hours could have done so more likely due to circulatory cause, introducing selection bias to this analysis.

Copeptin at all timepoints was independently associated with cardiovascular deterioration, indicating a statistically robust association with the patients' hemodynamic status. The OR's for copeptin and cardiovascular deterioration was however very close to one, indicating no value for routine clinical use.

Circulatory shock (Paper III)

The main finding in this paper is that circulatory shock on admission after cardiac arrest was found to be associated with poor neurologic outcome on hospital discharge.

Autoregulation is the innate mechanism regulating cerebral blood flow over a wide range of perfusion pressures, mitigating ischemia and hyper perfusion [224]. The lower limit of autoregulation, however, is right shifted after cardiac arrest [128]. This leaves cerebral blood flow reliant on blood pressure, rendering cerebral oxygenation vulnerable in hypotension. This process is further aggravated by cerebral hypoperfusion caused by microcirculatory injury [32], potentially explaining the pathophysiology of cerebral injury with hypotension after cardiac arrest.

The pathophysiological concept of circulatory shock is commonly used clinically in critical care medicine to describe patients with end organ hypoperfusion resulting in impaired cellular function due to dysoxia. In the absence of a uniform definition, most studies use surrogate hemodynamic markers of circulatory shock, usually hypotension. No evidence, however, has been published investigating the correlation between hypotension and circulatory shock after cardiac arrest. The European Resuscitation Council guidelines include blood pressure targets for hemodynamic optimalization after cardiac arrest, based on low quality of evidence [107]. Circulatory shock in the INTCAR registry is defined as signs of hypoperfusion, vasoactive support or systolic blood pressure < 90 mmHg. This definition, in theory, has higher sensitivity for end organ hypoperfusion, than hypotension alone.

In our main analysis we found that the odds for good neurologic outcome was 40% lower in patients with circulatory shock on admission in a model adjusted for early predictors of outcome and premorbid cardiovascular condition. The independent association of circulatory shock on admission after OHCA has not been reported before, but could be compared with estimates of outcome in studies investigating hypotension after OHCA [107,127,130-137,139,225-233], however, only seven of these studies investigated hypotension within the first few hours of in-hospital care [131,133,137,226,231-233], and three of them reported conflicting results on hypotension as an independent marker of outcome [226,231,232]. The diverging evidence is likely explained by model design, power, and population studied.

In our subgroup analysis, previous hypertension and circulatory shock on admission was associated with worse outcome. This is consistent with a right-shift in cerebral autoregulation with chronic hypertension [127,234], and suggests further studies targeting individual hemodynamic goals as a means of improving outcome.

Our findings should also be compared with studies investigating cardiac output as a predictor of outcome after cardiac arrests. Of the four relatively small observational studies [124,134,225,235] investigating this, only one reported a positive association of patient related outcome measures with increased cardiac output. Results from two small pilot trials involving hemodynamic interventions [113,138] were neutral regarding outcomes, underlining that causal inference regarding circulatory shock and outcome cannot be drawn from the current body of evidence.

Our analyses add to the evidence of using the clinical composite circulatory shock as an independent predictor of outcome after OHCA.

Vasopressor support (Paper IV)

Therapeutic targeted temperature management at 33ºC increase systemic vascular resistance and reduce cardiac output after OHCA [48]. It is not known whether this physiologic response could deteriorate tissue hypoperfusion in patients with vulnerable cardiac function and reduce survival.

We hypothesized that, the potential deleterious circulatory effects of induced hypothermia with subsequent rewarming, have minimal impact in patients with no circulatory failure (resilience) or major circulatory failure (established injuries to vital organ systems), but could influence outcomes for patients with marginal circulatory status without established injuries (at risk population). According to our theory, the dichotomous definition of circulatory shock, by definition will not be able to discriminate patients at risk. This could possibly explain the neutral results regarding the association of survival with temperature intervention for patients with circulatory shock on admission in the *post hoc* analyses from TTM-1 [160] and TTM-2 [41] trial.

Our primary analysis indicates that all-cause incidence of death was increased in patients with moderate circulatory support treated with targeted temperature management at 33ºC. It seems this effect was driven by an increase of non-neurological death.

The TTM-2 trial reported a higher degree of compromising arrhythmia with TTM33 [41], however, the relative risk of compromising arrhythmia with TTM33 did not differ with vasopressor support group in our analysis. The major differences in hemodynamic response to induced hypothermia with subsequent rewarming were: 1) No increase in heart rate for patients with vasopressor support after rewarming; 2) No decrease in blood pressure at rewarming for patients with No-VS; 3) High vasopressor support coincided with rewarming; 4) shorter duration of increase in blood pressure in groups with vasopressor support compared to No-VS; Lactate was minimally increased in all subgroups with an intervention at 33ºC.

These hemodynamic findings may be in support of a TTM33 associated increase in mortality for patients with Moderate-VS due to an induced relative bradycardia, resulting in decreased cardiac output and possibly lower perfusion pressure, both reducing cellular metabolism and function. Reduced ability to increase cardiac output with rewarming could also be aggravated by an inflammatory response [236] with accompanying increased risk of neurological or circulatory deterioration.

An increase in mortality in the group with Moderate-VS only is in line with our theory of patients at risk, however, this cannot be definitely concluded due to the low statistical power to detect a difference in mortality in the High-VS group.

Our results are in contrast to three observational registry studies of highly selected patients have investigated differential outcome with temperature management based on the severity of post cardiac arrest syndrome. In two Japanese studies targeted temperature management below 35ºC was associated with better outcome in a subgroup with higher degree of circulatory compromise at admission [237,238]. An American registry study [239] of an OHCA population without obvious severe brain injury, found survival higher with TTM33 in patients with Noradrenalin/adrenaline at admission □0.1 µg/kg/h, whereas TTM36 was associated with better outcome in patients with vasopressor dose below this level.

The results of our analysis are the first from a trial inferring potential harm with TTM33 in a subgroup of patients after OHCA.

Limitations

All studies in this thesis contain post hoc observational evidence without pre-published protocols, increasing the risk of bias. Additionally, because of the retrospective design, data capture was probably lower than would have been expected from prospective studies. Our data, nonetheless, stems from large populations, and in three of the papers from well controlled trials. Results were in line with sensitivity analyses, pathophysiological mechanism or previous findings. The analyses were exploratory and multiple analyses were not corrected for statistically, increasing the risk for type I error. Results, thus, should be considered supportive of previous findings or hypothesis generating. By virtue of design our results cannot infer causality.

Biomarkers lactate and copeptin (Paper I and II)

When analyzing surrogate markers of circulatory failure, we cannot rule out that the exclusion criteria of severe shock on admission could have confounded our results. Timing is critical when analyzing biomarkers. These samples were collected according to protocol, but theoretically selection bias could have been introduced, e.g. sampling not performed or performed at later time due to prioritized tasks in sicker patients, and in case of death not being sampled at all.

Circulatory shock (Paper III)

The definition of circulatory shock, could be viewed both as a strength, in that it includes the pragmatic clinical interpretation of circulatory status, and a limitation, because of the subjective definition. Since data is based on a registry with no information on screening failure, we cannot exclude the possibility of selection bias. The data in this registry has not been extensively monitored, adding to the risk of random error and bias. Our analysis was based on neurologic status at hospital discharge. It is possible that some patients improved beyond that timepoint, potentially adding risk of a type II error to our analysis. The explained variance for outcome in the regression model was low, indicating influential variables not included in our model, or poor quality/noise in our dataset.

Vasopressor support and hypothermia (Paper IV)

Patients dying from circulatory cause of death, might also have sustained major brain injuries not compatible with life, thus possibly only short time survival is affected by temperature intervention in the Moderate-VS group, possibly explaining the barely significant results in primary analysis. Because of low *post hoc* power to discriminate survival with temperature intervention, we do not have the evidence to support our categorization of patients at risk for poor outcome based on vasopressor support on admission.

Conclusions

Lactate

- Admission lactate and 12-hour lactate values were independently associated with short time survival after OHCA.
- The clinical value of lactate as a sole predictor of outcome after OHCA was limited and routine use for prognostication after cardiac arrest cannot be recommended.

Copeptin

- Copeptin at 24 hours after out-of-hospital cardiac arrest is an independent marker of short time survival and circulatory cause of death
- Copeptin is independently associated with progression of circulatory failure.

Circulatory shock

- Circulatory shock at hospital admission after OHCA is independently associated with poor neurologic outcome at hospital discharge.

Vasopressor support and induced hypothermia

- Induced hypothermia to 33ºC with subsequent rewarming after OHCA, compared to normothermia and early treatment of fever, was associated with higher incidence of death in patients with moderate vasopressor support at admission.
- The increase in death with TTM33 in the moderate vasopressor support group was related to an increase in non-neurological death.

Future aspects

Circulatory failure and outcome after out-of-hospital cardiac arrest

A recent study clustering septic shock patients using hemodynamic variables revealed five different shock phenotypes with different pathophysiologic mechanisms and significantly different outcomes [240]. It seems reasonable to assume that circulatory failure after OHCA consists of sub-phenotypes since circulatory shock precipitated by cardiac arrest and sepsis share common traits [162], implying that the concept of circulatory failure does not have enough granularity to be used to direct individual therapy.

Future efforts should include classifying circulatory failure in sub-phenotypes and explore their pathophysiology, evolution over time/therapeutic interventions, interaction with patient characteristics and their impact on outcome.

This could be done in the setting of a prospective multicenter cohort study using a definition of circulatory failure with a high sensitivity for detecting cellular dysoxia by means of clinically available findings and biomarkers. The major challenge in such research would be to collect high-quality data in a timely fashion using advanced, and sometimes operator dependent, hemodynamic parameters (i.e. echocardiography) in a large population.

Circulatory failure and targeted temperature at 33ºC

The finding that TTM33 is associated with incidence of death in patients with moderate vasopressor support is relevant since the current ESICM-ERC guidelines [152] does not preclude mild therapeutic hypothermia in certain subpopulations. This finding needs to be scrutinized in future studies involving a temperature intervention after OHCA.

Further research in this field could be designed to include a higher temporal resolution for vasopressor dose and hemodynamic data, enabling categorization of circulatory failure as exposure over time, and a better understanding of the pathophysiologic mechanism involved in the evolution of non-neurological cause of death. Including neurospecific biomarkers in analysis to estimate the competing hazards of neurological injury in relation to circulatory cause of death is needed for estimating outcome in a more patient centered approach.

Summary in Swedish

Ungefär 6000 svenskar drabbas av hjärtstopp utanför sjukhus årligen, de flesta av cirka 600 överlevare återhämtar sig väl. Merparten av drabbade, cirka 65%, är män i övre medelåldern med tidigare hjärtsjukdom.

Bakomliggande orsak och initial hjärtrytm är förenade med överlevnad. Sannolikheten att överleva är även starkt beroende av cirkulationsstilleståndets varaktighet, varför tidig upptäckt och behandling samt hjärtlungräddning och defibrillering är kopplade till ökad överlevnad.

Kroppens celler erhåller syrgas från lungorna via blodet, för att omvandla näringsämnen till energi. Vid cirkulationsstillestånd uppstår snabbt energibrist vilket bland annat föranleder allvarliga skador på cellernas jonkanaler, frisättning av fria syreradikaler, ökad mjölksyraproduktion, aktivering av koagulation och inflammationssystem samt programmerad celldöd.

Hjärnan saknar energidepåer och är särskilt känslig för dessa sjukdomsprocesser. Funktionen slås ut inom en halv minut, och återupprättas inte syrgasleveransen till hjärnan blir skadorna bestående inom några minuter. Merparten av hjärtstopps patienter förblir medvetslösa den närmsta tiden efter cirkulationsstoppet. Även efter att syrgasleverans återupprättas fortgår skador på kroppens vitala organsystem på grund av de sepsis-lika kaskadreaktioner som initierats i samband med syrebrist. Cirkulationssvikt uppstår då även hjärtats och blodkärlens funktion blir påverkade av dessa processer, vilket leder till ytterligare minskad syrgasleverans till känsliga organsystem.

Merparten av patienter som avlider efter hjärtstopp dör då botande behandling avbryts på grund av allvarliga hjärnskador som ej är förenliga med medvetande, cirka 25% av dödsfallen orsakas dock av skador på andra organsystem, framför allt cirkulationssystemet.

Sedan drygt 20 år har patienter behandlats med nedkylning efter hjärtstopp. Tanken bakom denna behandling har varit att minska hjärnans energibehov i en bristsituation, men även minska de skadliga processer som driver utveckling av ytterligare skador efter återupprättad cirkulation. De senaste 10 åren har denna behandling blivit alltmer ifrågasatt då det inte finns några starka bevis för att behandlingen fungerar. Kylbehandling kan teoretiskt öka stressen på hjärtat och på så vis ha negativ effekt på överlevnad.

Det finns ingen objektiv, tydlig definition av cirkulationssvikt. Allvarlighetsgraden skiljer sig åt mellan patienter, vilket gör det svårt att studera effekten av given behandling då den kan vara beroende av graden av cirkulationssvikt. Syftet med denna avhandling har varit att fastställa hur olika markörer för cirkulationssvikt förutspår utgången efter hjärtstopp. Detta har gjorts genom att analysera data från medvetslösa vuxna patienter som drabbats av medicinsk orsak till hjärtstopp utanför sjukhus. Samtliga patienter har varit inkluderade i patientregister eller studier som inte specifikt är skapade för våra analyser:

Mjölksyra i blod har visat sig vara kopplat till överlevnad i sjukdom relaterat till sepsis eller trauma. Eftersom mjölksyra produceras som svar på syrebrist i kroppens vävnader bör nivån svara mot allvarlighetsgraden cirkulationssvikt i samband med hjärtstopp. Våra resultat visade att mjölksyra vid ankomst var förenat med överlevnad, men att precisionen för att förutspå överlevnad är för dålig för att tillämpa kliniskt.

Antidiuretiskt hormon (ADH) är ett potent kärlsammandragande hormon frisatt från hypofysen. Copeptin frigörs från en gemensam molekyl vid utsöndring av ADH. Copeptin är förhöjt vid cirkulatorisk svikt vid tex hjärtinfarkt och hjärtsvikt. I vår analys förutspår copeptin, analyserat ett dygn efter hjärtstopp, överlevnad, cirkulatorisk försämring och cirkulatoriskt orsakad död.

Cirkulatorisk chock, definierat som systoliskt blodtryck <90 mm Hg eller kliniska tecken till dålig cirkulation, eller behov av läkemedel för att stötta hjärt/kärl funktion vid ankomst efter hjärtstopp är förenat med sämre odds för bra neurologisk återhämtning i samband med utskrivning från sjukhus. Patienter som behandlats för kroniskt högt blodtryck innan hjärtstoppet hade sämre odds för bra neurologisk återhämtning om de hade cirkulatorisk chock vid ankomst jämfört med övriga patienter med cirkulatorisk chock.

Patienter med måttligt cirkulationsstöd efter hjärtstopp och nedkylning till 33ºC efter hjärtstopp löper ökad risk för död inom 6 månader jämfört med patienter som ej behandlats med kylbehandling. Den ökade dödligheten i denna grupp förefaller vara driven av cirkulationsorsakad död.

Med ökad kunskap om bakomliggande mekanismer i samband med sjuklighet och död i samband med kritisk livshotande sjukdom framgår det allt tydligare att dessa patienter utgör ett brokigt urval. ”One size fits all”-konceptet gällande samma behandling till alla är inte rimligt, utan framgångsrik behandling måste anpassas till den individuella patientens behov. Denna typ av behandling är sedan länge etablerad inom exempelvis onkologi, och har svarat för mycket av den ökade överlevnaden vid cancersjukdomar. Det är därför viktigt att fortsätta arbetet med att karakterisera olika typer av cirkulationssvikt och effekten av behandlingar i dessa undergrupper i samband med hjärtstopp.

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