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Cardiac arrest – prognostic biomarkers and aspects of shock

Annborn, Martin

2014

Link to publication

Citation for published version (APA):
Annborn, M. (2014). *Cardiac arrest – prognostic biomarkers and aspects of shock*. [Doctoral Thesis (compilation), Anesthesiology and Intensive Care]. Anaesthesiology and Intensive Care.

Total number of authors:
1

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Cardiac arrest

– Prognostic biomarkers and aspects of shock

Martin Annborn

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DOCTORAL DISSERTATION
By due permission of the Faculty of Medicine, Lund University, Sweden

To be defended at Segerfalkssalen, Wallenberg Neurocentrum, Sölveg. 17, Lund
on Thursday, December 11, 2014 at 09.00 a.m.

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Co-tutors

Professor David Erlinge

Med. Dr. Niklas Nielsen

Organization	**Document name**
LUND UNIVERSITY	DOCTORAL DISSERTATION
Department of Clinical Sciences, Anaesthesiology and Intensive care	**Date of issue** December 11th, 2014
Author(s) Martin Annborn	Sponsoring organization

Title and subtitle: Cardiac arrest: prognostic biomarkers and aspects of shock

Abstract

Background: Some improvement has been seen in survival after cardiac arrest but the outcome is still poor and 50-70% of patients do not survive despite successful return of spontaneous circulation (ROSC). The cause of death is multifactorial. The majority of patients die from brain injury, but up to 35% die as a result of circulatory failure.
Purpose: First, to investigate the release profiles of an array of biomarkers in patients treated with mild induced hypothermia after cardiac arrest and study their correlation to the post-cardiac arrest syndrome (PCAS) and long-term outcome; Second, to investigate the effect of two different target temperatures (33°C and 36°C) on hemodynamics and vasopressor requirement in cardiac arrest patients and; Third, to investigate the association of target temperature with outcome in patients with shock in admission.
Methods: The biomarkers were collected serially at 8 time points during the first 72 hours following cardiac arrest in 84 still comatose post-resuscitation cardiac arrest patients treated with mild induced hypothermia. We analysed markers of inflammation; procalcitonin (PCT) and c-reactive protein (CRP), oxidation; peroxiredoxin 4 (prx4), cardiac stress; MR-proANP, cardiac injury; Troponin T (TnT), brain injury; Neuron specific enlolase (NSE), and the stress hormone; CT-proAVP (copeptin). Outcome was assessed at 6 months with the cerebral performance category scale (CPC) where CPC 1-2 was considered a good outcome. The cardiovascular sequential organ failure assessment score (SOFA-score) and the time to ROSC were used as surrogate markers for the PCAS. Three different definitions of infection were used to assess occurrence of infection.
The effect of a target temperature of 33°C or 36°C on hemodynamics was investigated in all patients with available vasopressor data (n=920) in the 'Targeted temperature management at 33°C versus 36°C after cardiac arrest' trial and in patients with shock on admission (n=139). Primary outcome was mortality. Secondary outcomes were vasopressor requirements as assessed by the cardiovascular SOFA-score, serum lactate concentrations, mean arterial pressure, and heart rate.
Results: PCT, CT-proAVP and MR-proANP were all significantly higher in patients with poor outcome and correlated to surrogate markers of the PCAS. No specific cut-off levels were identified. PCT release was not associated to infection. Combinations of biomarkers may be a promising concept to improve prognostication. A targeted temperature of 33°C was associated with increased vasopressor requirements and increased lactate levels in both our investigated cohorts. A low MAP during the intervention (0-36 hours) was associated with poor outcome after adjustment for baseline characteristics.
Conclusion: Biomarkers from other sources than the brain are associated to the PCAS and may be promising biomarkers to prognosticate outcome, alone or in combination. Targeted temperature management at 33°C is associated with increased vasopressor requirements and severity of shock and does not improve outcome as compared to 36°C.

Key words Cardiac arrest, shock, outcome, prognostication, post cardiac arrest syndrome, hypothermia

Classification system and/or index terms (if any)

Supplementary bibliographical information | **Language** English

ISSN and key title 1652-8220 | **ISBN** 978-91-7619-069-2

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Cardiac arrest

– Prognostic biomarkers and aspects of shock

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Lund University, Faculty of Medicine, Doctoral Dissertation, Series 2014:140

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ISBN 978-91-7619-069-2
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2014

“Success is going from failure to failure without losing your enthusiasm.” *~ Winston Churchill*

To my family

Table of contents

Original papers

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

I. Annborn M, Dankiewicz J, Erlinge D, Hertel S, Rundgren M, Smith JG, Struck J, Friberg H. Procalcitonin after cardiac arrest - an indicator of severity of illness, ischemia-reperfusion injury and outcome. Resuscitation. 2013 Jun; 84(6): 782-7.

II. Annborn M, Dankiewicz J, Nielsen N, Rundgren M, Smith JG, Hertel S, Struck J, Friberg H. CT-proAVP (copeptin), MR-proANP and Peroxiredoxin 4 after cardiac arrest: release profiles and correlation to outcome. Acta Anaesthesiol Scand. 2014 Apr; 58(4): 428-36.

III. Annborn M, Bro-Jeppesen J, Nielsen N, Ullén S, Kjaergaard J, Hassager C, Wanscher M, Hovdenes J, Pellis T, Pelosi P, Wise MP, Cronberg T, Erlinge D, Friberg H; TTM trial investigators. The association of targeted temperature management at 33 and 36 °C with outcome in patients with moderate shock on admission after out-of-hospital cardiac arrest: a post hoc analysis of the Target Temperature Management trial. Intensive Care Med. 2014 Sep; 40(9):1210-9.

IV. Bro-Jeppesen J, Annborn M, Hassager C, Wise MP, Pelosi P, Nielsen N, Erlinge D, Wanscher M, Friberg H, Kjaergaard J; TTM trial investigators. Hemodynamics and vasopressor support during targeted temperature management at 33°C versus 36°C after out-of-hospital cardiac arrest. Crit Care Med. 2014 Oct 31; [Epub ahead of print]

V. Annborn M, Nilsson F, Dankiewicz J, Nielsen N, Rundgren M, Hertel S, Struck J, Friberg H. The combination of biomarkers for prognostication of long-term outcome in patients treated with mild hypothermia after out-of-hospital cardiac arrest. In manuscript.

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Abbreviations

AMI	Acute myocardial infarction
AUC	Area under the curve
CAG	Coronary angiography
CI	Confidence interval
CBF	Cerebral blood flow
CPIS	Simplified clinical pulmonary infection Score
CPC	Cerebral performance categories
CPP	Coronary perfusion pressure
CPR	Cardiopulmonary resuscitation
CRP	C-reactive protein
CT-proAVP	C-terminal provasopressin (copeptin)
ECG	Electrocardiographic recording
ERC	European resuscitation council
IABP	Intra-aortic balloon pump
ICP	Intracranial pressure
ICU	Intensive care unit
IHCA	In-hospital cardiac arrest
ILCOR	International liaison committee of resuscitation
INTCAR	International cardiac arrest registry
MAP	Mean arterial pressure
MR-proANP	Mid regional proatrial natriuretic peptide
NPV	Negative predictive value
NSE	Neuron specific enolase

OHCA	Out-of-hospital cardiac arrest
PCAS	Post cardiac arrest syndrome
PCI	Percutaneous coronary interventions
PCT	Procalcitonin
PEA	Pulseless electrical activity
PPV	Positive predictive value
Prx4	Peroxiredoxin 4
RCT	Randomised controlled trial
PRMD	Post cardiac arrest myocardial dysfunction
ROC	Receiver operating characteristic
ROSC	Return of spontaneous circulation
SOFA	Sequential organ failure assessment
SSEP	Somatosensory evoked potentials
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

Ischemic heart disease is the most common cause of death in the world according to the World health organisation killing 7.4 million people per year [1]. In Sweden approximately 5,200 people had a registered out-of-hospital cardiac arrest (OHCA) where resuscitation was attempted in 2013 and 539 were alive one-month later [2]. The survival has steadily improved in recent years, probably due to better awareness of impending signs of cardiac arrest among laypersons, higher frequency of bystander cardiopulmonary resuscitation (CPR), and improved hospital care [3].

Short time to return of spontaneous circulation (ROSC) is of uttermost importance for the cardiac arrest patient since ischemic cellular damage rapidly becomes irreversible. The ischemia and subsequent reperfusion results in a generalised inflammatory response [4]. This so called post cardiac arrest syndrome (PCAS) consists of brain injury, myocardial damage, and multiple organ failure [5] with less than 50% chance of survival [6, 7]. One of the few therapeutic options that is believed to attenuate the PCAS and improve survival is induced mild hypothermia at 33°C [8, 9], but this was challenged in by a recent publication showing no difference in outcome between a target temperature of 33°C as compared to 36°C [10]. Furthermore, little is known about the effects on hemodynamics of induced mild hypothermia although lowering the temperature is generally considered safe, even in patients with shock on admission [11-15].

Much research in post-resuscitation cardiac arrest care has focused on prognostication of outcome in comatose patients. Currently, no consensus exists of which methods to use and when prognostication should be done following cardiac arrest but most agree on a multimodal approach using several prognostic tools [16-18]. Whether prognostication could be performed at 72 hours after cardiac arrest or should be delayed further is also debated. Biomarkers are often included in prognostication and the most commonly used is the brain-derived biomarker Neuron specific enolase (NSE). Recent studies, however, observed differences in reported concentrations due to analysis method [19, 20] and no reliable cut-off concentrations for poor outcome have been identified [21-23]. This has spawned interest in the search for other biomarkers from other origins than the brain to be used in prognostication, possibly in combination with NSE.

This thesis focuses on two aspects of post-resuscitation care in cardiac arrest patients; first, the relevance of an array of biomarkers, some tested for the first

time for prognostication of outcome and how they correlate to the ischemia-reperfusion injury, and second, what effect targeted temperature management at 33 or 36°C have on vasopressor requirement, hemodynamics, and outcome in cardiac arrest patients in general and in the subgroup of patients with shock on admission.

Background

Cardiac arrest

All animals die of biological ageing with few exceptions. Dying is a biological process and death is the ultimate event in that process. Most laypersons consider death as the moment when the dying person´s last breath has transpired and the heart stops beating.

According to Swedish law and many other legal systems in the world, death is defined by the complete and irreversible loss of total brain function [24]. Thus, the heart can function normally and breathing can artificially be sustained with a respirator whilst the patient is dead. Conversely, death after cardiac arrest only ensues because of the anticipated loss of total brain function after the blood circulation to the brain has ceased. The duration from the last heartbeat to the pronunciation of death has not been clearly defined in Swedish law, but the physician must be certain that sufficient time has passed to ensure the complete and irreversible loss of all brain functions.

Physiology of cardiac arrest

Weisfeldt and Becker described three phases following cardiac arrest: 1) an *electrical phase* lasting for about four minutes following cardiac arrest when defibrillation alone may suffice to restore the circulation, 2) a longer *circulatory phase* where chest compressions are needed to restore the possibility that defibrillation will lead to an effective circulation, and 3) the *metabolic phase* that offers no chance of successful resuscitation with current therapies [25]. When 20-30 minutes has passed without effective treatment, the changes in the myocardium become irreversible and the heart sometimes manifests this with one final agonal contraction – 'stone heart' [26].

During the first 30 seconds following cardiac arrest the average arterial blood pressure falls rapidly to very low levels while the central venous pressure gradually rise, but it takes 4-5 minutes before an equilibrium between the arterial and venous circulation has been reached and the forward flow ceases [27, 28]. This redistribution of blood volume to the venous circulation increases the right

ventricular volume and this dilation can be visualised in experimental open chest preparations [28], and in MRI observations with an intact pericardium [29]. The coronary perfusion pressure (CPP), defined as the pressure gradient between the aortic and right atrial pressure during diastole, falls rapidly if no resuscitative attempts are made [30, 31]. Even short interruptions in mechanical chest compressions reduce CPP and coronary blood flow velocity, which in turn reduce the possibility that defibrillation will yield effective contractions and circulation. An adequate CPP is correlated to the rate of successful ROSC [28, 32].

Cardiac arrest induces a massive neurohumoral response with 30- to 300-fold elevations in endogenous plasma concentrations of noradrenalin and adrenalin during CPR [33]. During the first 60 minutes of the immediate post-resuscitation period these levels remain markedly elevated with values typically more than 1000% of those measured prior to cardiac arrest [34].

Types of cardiac arrest

Primary rhythm

Cardiac arrest implies that contractility of the heart muscle is lost. The electrical rhythms as seen on the first electrocardiographic recording (ECG) can, however, be of different categories: Shockable rhythms are those that can be converted into sinus rhythm by defibrillation and includes ventricular fibrillation (VF) and ventricular tachycardia (VT). Unshockable rhythms are asystole and pulsless electrical activity (PEA). Asystole has to be converted to a shockable rhythm through resuscitative attempts and then defibrillated to an organised rhythm. PEA, on the other hand, has an ECG reading that normally should provide adequate circulation but does not. The distinction between PEA and severe cardiogenic shock may be hard to define [35, 36].

Location

If the cardiac arrest occurs outside the hospital it is termed OHCA and if it occurs inside the hospital, in-hospital cardiac arrest (IHCA). This distinction is important since the pathological process causing the arrest is often different and so is the outcome.

Aetiology

A cardiac cause is presumed to be the aetiology in 65-89% of all OHCA where resuscitation is attempted [2, 37-39]. Of the cardiac causes acute myocardial ischemia is the most common, followed by non-atherosclerotic disease of the coronary arteries, cardiomyopathies, and valvular heart disease. The most frequent non-cardiac causes of OHCA are trauma, non-traumatic bleeding, pulmonary embolism, suicide, lung disease, malignancy, and drug overdose [35].

IHCA is more often the result of a protracted clinical deterioration from critical illness and less often from acute myocardial ischemia as compared to OHCA [40, 41].

Epidemiology

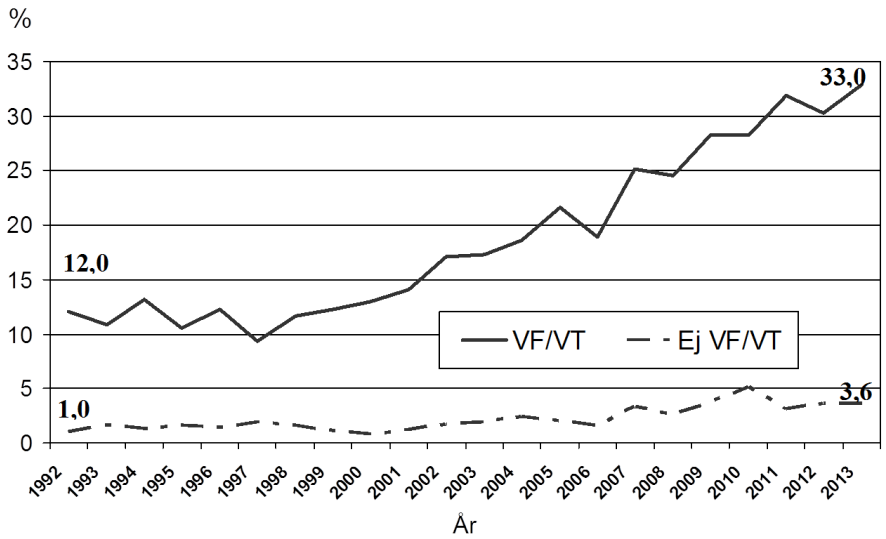
Out-of-hospital cardiac arrest

It is estimated that in Europe 275,000 people suffer every year from sudden cardiac arrest and 29,000 are resuscitated and survive [42]. Women have a lower incidence as compared to men [2, 43, 44]. In Sweden, 5,210 people had a registered cardiac arrest where resuscitation was attempted in 2013 [2]. The incidence was 52 per 100,000 inhabitants, which is similar to international reports of 38-54 per 100,000 inhabitants [2, 42, 45]. Since the start of 'the national Swedish register for cardiac arrest' in 1992 there has been an increase in patients admitted alive to hospital, from 15 to 25%, and in one-month survival, from 4.8 to 10.6%, which is in analogy with international reports [2, 42, 45]. This improved survival is largely due to increased survival for patients with a shockable primary rhythm although an increase in survival is also seen with non-shockable rhythms (Figure 1) [2]. Nighty-three percent of discharged patients in the registry had a good outcome with a cerebral performance category (CPC) of 1-2 [2].

The reason for the improved survival is not entirely evident but several factors are plausible. More patients are treated with bystander CPR before the ambulance crew arrival. Forty-percent in 1992 as compared to 70% in 2013, which are among the highest numbers in the world [2]. There has also been an increased interest in the care of resuscitated cardiac arrest patients after arriving to the hospital with increased frequency of coronary angiography (CAG) and improved intensive care [2]. Finally, more cardiac arrests are witnessed by the ambulance crew indicating better awareness in the general public and by emergency dispatchers of the symptoms of severe cardiac disease. Unfortunately, the response time (from alarm to arrival at the scene for the ambulance) has increased from 6 to 10 minutes, although the time from cardiac arrest to first defibrillation is roughly the same (12 minutes) [2]. The reason for this contradiction is probably due to the increased availability of defibrillators in public areas and the involvement of fire and rescue services by dispatchers in in medical emergencies.

A 35-year old man with a witnessed cardiac arrest with a first monitored ventricular fibrillation had a 43% one-month survival [2] as compared to almost zero probability of survival if the cardiac arrest was unwitnessed with a non-shockable rhythm, and no bystander CPR was performed [46, 47].

Figure 1. One-month survival dichotomized into shockable (VF/VT) and non-shockable rhythms (asystole/pulseless electrical activity) in patients with cardiac arrest where resuscitation was attempted beteween 1992 and 2013 in Sweden.



From 'Nationellt register för hjärtstopp, årsrapport 2014. National Swedish register for cardiac arrest (in Swedish)', by Herlitz, J. 2014 © Svenska rådet för hjärt- lungräddning. Reprinted with permission.

In-hospital cardiac arrest

The reported incidence of IHCA is more variable, but it is in the range of 1-5 per 1000 admissions [48]. In 2005, 'The national Swedish register for cardiac arrest' started analysing IHCA and now include 90% of Swedish hospitals. The yearly report shows that in 2013, 50% of patients had ROSC and the overall survival to hospital discharge was 28%, which is comparable with most international studies [2, 49, 50]. The reported survival differs largely between participating hospitals, ranging from 20 to 43%, and might in part be due to different implementation of do-not-resuscitate protocols. The survival was markedly higher depending on the location of the arrest with better survival in the coronary angiography laboratory, operating theatre, and cardiac intensive care unit as compared to the wards [2]. This probably reflects different causes of the cardiac arrest but also the fact that the patients are monitored to a larger extent in these locations. The outcome for patients who were discharged alive was equally good as in OHCA with a CPC 1-2 in 94% [2].

Cardiopulmonary resuscitation

History

Already in 1740 the Paris academy of sciences recommended mouth-to-mouth resuscitation for drowning victims. In 1954 James Elam was the first to demonstrate experimentally that mouth-to-mouth rebreathing was a sound technique and in collaboration with Peter Safar demonstrated that it was superior to previous methods of chest-pressure arm-lift [51]. In legendary experiments volunteer colleagues, medical students, and nurses were paralyzed with curare and artificially ventilated for hours using mouth-to-mouth ventilation to prove the methods´ effectiveness [52, 53]. In 1957 Safar wrote the book ABC of resuscitation, which was promoted as a technique for the public to learn in the 1970s.

Friedrich Crile reported in 1903 the first successful use of external chest compressions in human resuscitation and in 1960 Kouwenhoven and colleagues published a report of the successful use of closed chest massage in 20 patients with IHCA showing a 70% survival rate [54]. The first CPR guidelines were published in 1966 by the American Heart Association [55].

In the 1930s it was known that electric shocks could introduce ventricular fibrillation and more powerful shocks could reverse fibrillation in dogs. In 1947 Claude Beck published a report of successful open chest massage and internal electrical defibrillation in a 14-year-old boy during surgery [56], in 1956 Paul Zoll and co-workers published a series of successful external defibrillations in patients with cardiac arrest [57], and in 1964 Paul Lown constructed a portable device bringing the possibility of defibrillation to the patient [58].

Education

The international liaison committee on resuscitation (ILCOR) was formed in 1992 to provide a forum for liaison between principal resuscitation organisations worldwide and to coordinate all aspects of cardiopulmonary and cerebral resuscitation. The European Resuscitation Council (ERC), the American Heart Association (AHA), and the Japanese Resuscitation Council published the current resuscitation guidelines in 2010 [59, 60]. The guidelines are updated every five years, next time in 2015. In Sweden, the national resuscitation council principally adopts the ERC guidelines and organizes education of ‘CPR instructors’ who in turn educate professionals and lay persons to perform CPR.

Chain of survival

The actions linking the victim of sudden cardiac arrest with survival are called the Chain of survival (Figure 2). The first link of this chain indicates the importance of recognising those at risk of cardiac arrest and calling for help. The

second and third link depicts the integration of CPR and defibrillation as the fundamental components of early resuscitation in an attempt to restore circulation. The guidelines main objectives are the reduction of the 'no-flow' time (time from the cardiac arrest to beginning of CPR), the improvement of the quality of CPR during the 'low-flow' time (time from beginning of CPR to ROSC), and the shortening of time to the first defibrillation attempt. Immediate CPR can increase survival by 2-3 times after VF OHCA [61-63]. Following VF OHCA CPR plus defibrillation within 3-5 minutes of collapse can yield survival rates as high as 49-75% [64-66] and each minute of delay before defibrillation reduces the probability of survival to discharge by 10-12% [62, 63].

The final link in the chain is post-resuscitation care that targets early recognition of the critically ill patient by medical emergency or rapid response teams, aims for preserving the functions of the heart and brain during ICU care, and the importance of avoiding secondary injuries.

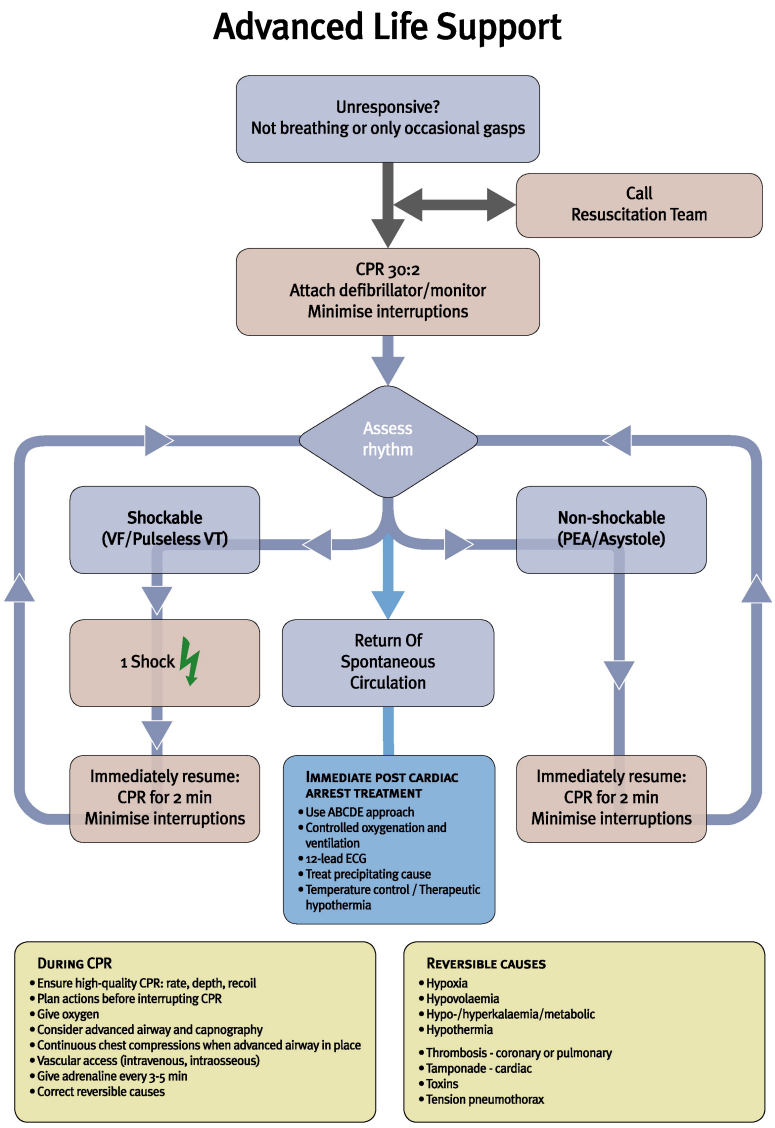
Figure 2. The chain of survival

From 'European Resuscitation Council guidelines for Resuscitation 2010 Section 4. Adult advanced life support', by Deakin CD, et al. Resuscitation 2010: 81;1305-1352. © Elsevier Ireland Ltd. Reprinted with permission.

Algorithm

It is important to recognize the two groups of heart rhythms associated with cardiac arrest: shockable (VF/VT) and non-shockable (asystole/PEA). The principal differences in the treatment of these two groups of arrhythmias are the need for defibrillation in those patients with VF/VT. There are also some minor differences in timing of adrenalin injections and the use of amiodarone between groups. All subsequent actions including chest compressions, lung inflations, secure airway management, vascular access, drug delivery, and the identification and correction of reversible factors are common to both groups (see Figure 3 for the advanced life support algorithm).

Figure 3. European Resuscitation Council advanced life support cardiac arrest algorithm



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Chest compressions

The chance of successful ROSC is declining with increasing length of ‘no-flow’ periods. The 2010 advanced ALS ERC algorithm (Fig. 3) emphasises the importance of high quality, uninterrupted chest compressions with continuation of

chest compressions while charging the defibrillator, and brief pauses only to enable specific interventions [60, 67]. The guidelines recommend 30 compressions, with 5-6 cm depth at the rate of 100-120 per minute with pause for two breaths of no more that 5 seconds [68]. If ventilation is not possible, chest-compression-only CPR can be adequate for the first minutes following cardiac arrest [69, 70].

Optimal chest compressions can at best deliver 30% of normal cardiac output [71] and a mean arterial blood pressure (MAP) of 40 mm Hg [72], which can provide sufficient circulation to vital organs for shorter time periods. Closed chest compressions generate their effect on the circulation by direct compression of the heart as well as by induced cyclic changes in intrathoracic pressure.

Mechanical compression and compression-decompression devices

It is well studied that rescuers rapidly fatigue when performing chest compressions [73]. Two mechanical systems have been tested in large clinical trials: The load-distributing band circumferential chest compression device (LDB-CPR) and the Lund university cardiac assist system (LUCAS®), a mechanical compression-decompression device. LUCAS® has in experimental and well-controlled settings demonstrated improved circulation with higher CPP and coronary blood flow velocity, enhanced cerebral blood flow, and higher end-tidal CO_2 pressure compared with manual CPR [32, 74-76]. These positive effects have, however, not translated into improved short-term survival in large RCTs for either device [77, 78].

Drugs

The evidence for using any medications to facilitate resuscitation following cardiac arrest is scarce. Despite the widespread use of adrenalin during resuscitation there is no placebo-controlled study that shows that the routine use increases neurologically intact survival at hospital discharge. The use of adrenaline is still, however, recommended based on animal data and reports of increased short-term survival in humans [60, 79-81]. The use of the anti-arrhythmic amiodarone in shock refractory VF improves short-term survival as compared to placebo or lidocaine and is recommended after the third defibrillation [60, 82, 83]. Other therapies used previously in guidelines, such as the routine use of bicarbonate and atropine is no longer recommended [84, 85].

The post cardiac arrest syndrome

Resumption of spontaneous circulation after prolonged complete whole-body ischemia is an unnatural pathophysiological state created by successful CPR. Vladimir Negovsky recognised the unique constellation of pathological processes and named this state postresuscitation disease in 1972 [86]. In 2008 ILCOR released a consensus statement and suggested a new term, the PCAS, to emphasise that resuscitation is still on-going and to avoid any admixing with CPR [5]. PCAS is complex and includes the following entities, 1) post-cardiac arrest brain injury, 2) post-cardiac arrest myocardial dysfunction, and 3) systemic ischemia-reperfusion response. This state is often complicated by a fourth component: the unresolved pathological process that caused the cardiac arrest. Although prolonged whole body ischemia initially causes global tissue and organ injury, additional damage occurs during and after reperfusion [87]. The severity of these disorders is not uniform and will vary in individual patients based on the severity of the ischemic insult, the cause of cardiac arrest, and the patient´s prearrest state of health. Usually, the shorter time to ROSC, the less severe is the PCAS.

The majority of research has focused on improving the rate of ROSC, and significant progress has been made [2]. Many interventions, however, improve ROSC without improving long-term outcome. This has encouraged the interest in improving medical care in the period following resuscitation in order to attenuate the effects of the PCAS. Also, some of the variation in survival after successful ROSC that has been described can possibly be attributed to inter-hospital variations in the level of hospital care [6, 7].

Brain injury

Brain injury is the most common cause of mortality after OHCA and accounts for 55-70% of all deaths in comatose patients after successful resuscitation from cardiac arrest [10, 88, 89]. Only about 10% of patients regain consciousness prior to hospital admission following cardiac arrest. In the remaining 90% there is a variable degree of injury to the brain and the final outcome can differ from complete recovery of pre-arrest cerebral function to variable neurologic deficits or worse, a vegetative state and brain death [88].

The adult human brain constitutes about 2% of body weight but extracts about one-fifth of all oxygen during rest. While many other tissues can manage for extended durations without an adequate oxygen supply through anaerobic metabolism, this possibility is limited in the brain. The complete cessation of blood flow to the brain leads to unconsciousness in 5-10 seconds as showed by Ralph Rossen and co-workes in 1943 [90]. In this study they investigated different

periods of total arrest of blood flow to the brain by deployment of the Kabat-Rossen-Andersson apparatus (a pressure cuff around the neck) in 126 volunteers and 11 schizophrenic patients, for as long as 100 seconds. This reflects the great metabolic demand of the brain and its vulnerability to ischemia.

In piglets, cardiac arrest resulted in progressive neurological damage that was most marked in the thalamus, followed by the cortex, hippocampus, hypothalamus, and the brain stem [91]. These results are consistent with human post-mortem data where one study investigated neuronal cell death in six different brain regions and showed greatest damage to the hippocampus and least damage in the brain stem [92]. The extent of the neuronal injury was also correlated to the inflicted ischemic damage (as measured by time to ROSC). Initially after cardiac arrest, many patients have an almost complete loss of clinical signs of brain function. During recovery, patients first regain brain stem reflexes followed by functions from higher centres. Clinically, patients with minor sequele can have emotional disturbances, short-term memory difficulties, or sensory, motor and/or cognitive disturbances correlating to injury in the thalamus, hippocampus, and cortex, respectively.

The brain injury following resuscitation from cardiac arrest can result from either global or focal cerebral ischemia. In global ischemia there is a reduction in cerebral blood flow (CBF) in the entire brain. Normal CBF is 50 to 75 ml per 100 g of brain tissue per minute. Ischemia occurs when CBF decrease to about 18 ml and neuronal cell death ensues if CBF is less than 10 ml per 100 g of brain tissue per minute. In focal ischemia, the ischemic vascular bed compromises an area with severe CBF reduction that consists of an ischemic centre and a surrounding ischemic penumbra.

In both global and focal ischemia, cell death is thought to result from two processes of neuronal cell death. Apoptosis, or programmed cell death, a process associated with genomic fragmentation, is characterised by cell shrinkage, chromatin aggregation, and preservation of cell membrane integrity without inflammation and injury to the surrounding tissue [93]. Necrosis, on the other hand, is a non-regulated process and is typically observed as a consequence of severe cerebral ischemia and characterised by disruption of cellular homeostasis, cellular swelling, and oedema formation. The relatively protracted duration of injury cascades and histological change suggests a broad therapeutic window for neuroprotective strategies following cardiac arrest [94].

In cardiac arrest, there is a variable duration of hyperaemia after ROSC that in turn is followed by a reduction in CBF to subnormal levels for at least 6-12 hours [95, 96]. Following prolonged cardiac arrest there can be areas of inhomogeneous blood flow causing small infarctions despite adequate CPP. One possible cause of these infarctions could be intravascular thrombosis. Attempts with thrombolysis have been promising in animal studies [97], but a larger RCT was negative both regarding survival and neurological outcome [98]. Cerebral

autoregulation is lost in a period following ROSC and varies with CPP instead of being linked to neuronal activity [99]. There have been animal studies indicating improved outcome if mean arterial pressure (MAP) is high and supra-normal cerebral perfusion pressure is achieved but RCTs are lacking [100]. One small trial in 10 cardiac arrest patient found no effect in non-invasive cerebral tissue oxygenation with induced hypertension [101], while observational studies show conflicting results [102, 103]. Others have studied the effect of the calcium blocker nimodipine as an adjunct to increase CBF but found no effect on outcome in 52 cardiac arrest patients [104].

Transient brain oedema can be observed early after ROSC but is rarely associated with clinically relevant increases in ICP. A minority of patients become brain dead, reported incidence varies from 5-12% of deceased patients if considering mixed aetiology and location of arrest. Although a small group, it is important to identify these patients since organ donation might be a possibility [88, 105]. Characteristics for these patients were young age (≥40 years old) and long times to ROSC.

Other factors that can impact the extent of inflicted brain damage after cardiac arrest are hyperglycemia, pyrexia, and seizures [5]. Hyperglycemia is common and is associated with poor neurological outcome and exacerbated ischemic brain injury that can be mitigated with insulin therapy [7, 106, 107]. Pyrexia is correlated to poor outcome and for each degree Celsius higher than 37°C, the risk of an unfavourable neurologic recovery increases [108].

Myocardial dysfunction

Post-cardiac arrest myocardial dysfunction adds to the low survival after cardiac arrest. If including all patients that die from post cardiac arrest shock, which also includes deaths from multiple organ failure, as many as 55% of deaths [109] could be attributed to a cardiac cause, although other reports are more conservative [10, 88, 89, 105]. Immediately following resuscitation there is normally a transient increase in catecholamine levels resulting from iatrogenic administration of adrenalin during CPR and from endogenous liberation due to stress [34]. Also, blood pressure can be extremely variable and other common hemodynamic end-points; such as lactate concentrations and central venous saturation are unreliable. To detect cardiac dysfunction advanced hemodynamic monitoring is required.

Laurent and co-workers described a reversible decline in cardiac index in patients with OHCA lasting for 24 hours in combination with a concomitant vasodilation up to 72 hours [110]. If cardiac function failed to improve by 24 hours, all patients died from multiple organ failure. In swine the ejection fraction decreased from 55 to 20% as early as 30 min following ROSC [111]. No reduction

in coronary blood flow was observed, indicating a true stunning phenomenon rather than permanent injury or infarction [112]. When treated with a dobutamine infusion, there was a dramatic improvement in left ventricular ejection fraction and diastolic dysfunction [111].

Ischemia-reperfusion injury

Cardiac arrest represents the most severe shock state, during which delivery of oxygen and metabolic substrates is abruptly halted and metabolites are no longer removed [5]. After this 'no-flow' phase, CPR is commenced creating a 'low-flow' state with a cardiac output of at best 30% of normal [71]. This period of inadequate oxygen delivery to the tissues creates an oxygen debt that can persist after ROSC if cardiac dysfunction is superimposed and persists in-hospital. The accumulated oxygen debt leads to a systemic inflammatory response similar to that from sepsis and is predictive of subsequent multiple organ failure and death [4, 113].

Almost immediately following ROSC there is an increase in various cytokines, soluble receptors, and endotoxins [4, 114]. Mediators of stress, such as CT-proAVP (copeptin) and inflammation, such as procalcitonin (PCT) are increased in blood already at admission to the ICU and reach higher concentrations in non-survivors [115-118].

Clinical manifestations of systemic ischemia-reperfusion response include intravascular volume depletion, impaired vasoregulation, and impaired oxygen delivery and utilisation [5]. No specific therapy has been proven to be effective in treating this diverse condition but target temperature management at 33 or 36°C is frequently utilised in comatose cardiac arrest patients and is considered to attenuate ischemia-reperfusion injury and improve outcome [8-10].

Biomarkers

Biomarkers are quantifiable biological substances, usually peptides, which can be collected and measured in different fluid compartments, most often blood. The ideal biomarker should be released in concentrations proportional to the inflicted injury and correspond to valuable clinical outcome parameters. It should be released immediately, preferably from a zero baseline and have a long half-life. The sample material should be easy to access and the assay should be immediately available, reliable, inexpensive, and not sensitive to confounding factors or interactions. Biomarkers are often used to diagnose disease and for severity assessment, risk assessment and monitoring of disease progress.

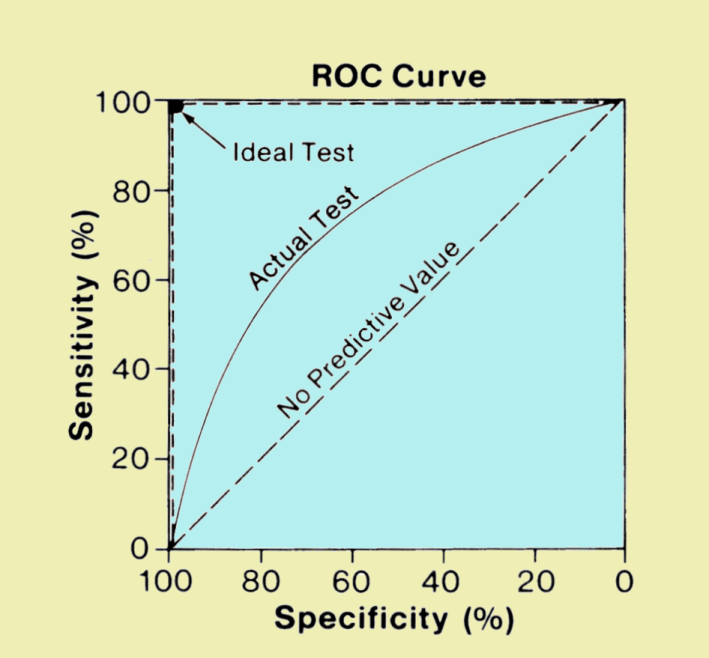
Biomarker statistics

Several statistical concepts are used to present a biomarker's performance in prognostication. Sensitivity and specificity are measures of the performance of a binary classification test. Sensitivity (true positive rate) measures the proportion of actual positives that are correctly identified by the test. Specificity (true negative rate) measures the proportion of actual negatives that are correctly identified as such. In the ideal situation, there are only true positives and true negatives. This would be a prognostic process with 100% accuracy.

This is not often the case in medicine because of inherent limitations of a specific test or biomarker. When describing the performance of a test or biomarker in prognostication of outcome, the accuracy can be defined as the false positive rate (1 – specificity) to predict poor outcome.

In general, if an observer is aggressive in trying to increase the number of true positives (sensitivity), the number of false negatives (decreased specificity) also increases. The relationship between sensitivity and specificity for a specific diagnostic test can be described by a graph known as a receiver operating characteristic (ROC) curve (Figure 4).

Figure 4. Reciever operating characteristic curve



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The ideal test or biomarker produces 100% sensitivity and 100% specificity as shown. If a test or biomarker has no predictive value, and a random selection process obtains outcome, the relationship between sensitivity and specificity is linear as shown in Figure 3. The clinician determines the actual operating point along this line and can 'choose' to increase specificity, at the expense of sensitivity.

Area under the curve (AUC) of the ROC curve is a single index for measuring the performance of a test. The larger the AUC, the better is overall performance of the test or biomarker to correctly identify patients with good or poor outcome. The 'ideal test' in figure 4 would have an AUC of 1 and the dotted line ('No predictive value') an AUC of 0.5. Equal AUCs of two tests represents similar overall performance of tests but this does not necessarily mean that both curves are identical.

Brain-derived biomarkers

Neuron specific enolase (NSE) is an intracellular glycolytic protein with a half-life of 30 hours. It is present in neurons and other cells of neuroectodermal origin. NSE can be used as a diagnostic biomarker in certain tumours such as neuroblastoma, small cell lung cancer, thyroid cancer, carcinoid tumours, endocrine tumours of the pancreas, and melanoma. Also, it is present in erythrocytes and is released with haemolysis, which can result in false positives when used for prognostication of poor outcome in comatose cardiac arrest patients.

NSE is the best-studied biomarker and has previously been incorporated into guidelines stating that a serum concentration >33 μmol/L at 48 hours after cardiac arrest is a reliable predictor of poor outcome [119]. After the introduction of hypothermia several studies reported higher cut-off concentrations (> 50-80 μmol/L) to avoid false positives, which has introduced uncertainty [21-23]. Instead of using a cut-off at a specific time point it has been suggested that trends are analysed. An increase of NSE between 24 and 48 hours has been associated with poor outcome and a decrease with good outcome [120-122].

Different assays are in commercial use for analysing NSE concentrations. Several recent publications have concluded that reported concentrations from the same blood sample could differ substantially between laboratories and between different commercial assays which has to be taken into account when NSE is used for prognostication [19, 20].

S-100B is glial specific and is expressed primarily in astrocytes. It is used in guidelines for initial management of traumatic head injury [123]. In cardiac arrest, high concentrations are associated with poor outcome but no reliable cut-off levels have been identified [121, 124]. In traumatic brain injury, S-100B release has been

observed in association with bone fractures without any evidence of concomitant brain injury [123]. So, S-100B could theoretically be released from fractures caused by chest compressions instead from the brain injury caused by hypoxia and thus interfering with S-100B´s prognostic accuracy. S-100B could, however, offer an advantage as compared to NSE since it has a shorter half-life and an earlier release profile.

Other potentially interesting and promising brain derived biomarkers include tau [125], glial fibrillary acidic protein [126], neurofilaments [127], and brain-specific micro-RNAs [128], but further research is needed.

Cardiac biomarkers

There has been limited interest in cardiac biomarkers for prognostication in cardiac arrest probably because cardiac cause of death is a less common mode of death [10, 88, 89].

Most investigations including cardiac biomarkers have been aimed at correctly diagnosing coronary occlusions in order to triage appropriate patients to coronary angiography. Troponin and high sensitive troponin assays show higher concentrations in patients with coronary occlusion but their predicative power isolated or in conjunction with ECG abnormalities has been disappointing in recent studies [129, 130]. This could be because of release from skeletal muscle and from myocardial damage due to chest compressions and defibrillations and not specifically from myocardial injury due to coronary occlusion. In 19 patients with non ST-elevation infarctions, elevations in CK-MB and Troponin I were seen after cardiac arrest, but values were low and rapidly reversible [131]. In 87 patients, CK-MB was correlated to AMI, longer time to ROSC, and cardiogenic shock while Troponin T showed no correlation other than to AMI [132]. As for other outcome measures, such as mortality and neurologic function no studies exist.

Procalcitonin

Procalcitonin, a 116 amino acid pro-hormone to calcitonin, is normally produced by the C-cells of the thyroid and by the neuroendocrine cells of the lung and intestine. The concentration of PCT in the blood of healthy individuals is usually below the lower limit of detection for clinical assays. In response to pro-inflammatory stimuli, especially by bacterial infections, PCT is increased several fold by a general release from all parenchymal tissues and differentiated cell types throughout the body [133, 134]. Upregulated PCT messenger ribonucleic acid (mRNA), synthesised by the calicitonin-I gene, has been shown to result in PCT

increase within 2-3 hours reaching a plateau within 6-12 hours with a half-life of 20-24 hours [135].

PCT has previously been investigated in cardiac arrest patients, both for diagnosing infection and for prognostication of outcome. Neither PCT nor C-reactive protein (CRP) were found to be useful biomarkers to diagnose infection the first days after cardiac arrest [136, 137]. Studies of clinical outcomes have included few patients, considered one single measurement point or suffered from other methodological problems [114-116, 118, 138]. Despite this, PCT is a promising biomarker that is elevated already at ICU admission suggesting a potential to use it for early prognostication or risk stratification.

CT-proAVP (copeptin)

CT-proAVP is the C-terminal fragment of the pro-vasopressin peptide, and is co-released from the hypothalamus via the posterior pituary gland, in equimolar concentrations as vasopressin upon hemodynamic or osmotic stimuli [139]. Vasopressin is difficult to analyse because of its short half-life and instability *in vitro*, while CT-proAVP is stable *in vitro* and can be analysed with a commercial kit [140].

CT-proAVP concentrations are elevated in patients with poor outcome in various diseases such as ischemic stroke [141], traumatic brain injury [142], heart failure [143], acute myocardial infarction (AMI) [144], pneumonia [145], and shock [139]. Furthermore, elevated CT-proAVP concentrations correlate with increasing severity of sepsis [139], pneumonia [145] and pre-eclampsia [146].

Previously, high vasopressin concentrations have been measured *during* advanced cardiopulmonary resuscitation in patients successfully resuscitated after OHCA [147], a finding implicating impaired neuroendocrine stress response in non-survivors. Kim and co-workers, on the other hand, showed that high vasopressin concentrations in patients with ROSC were associated with increased mortality at one month [148]. In a recent publication, a correlation between high CT-proAVP concentration at admission to the ICU after OHCA and poor outcome was reported [117].

Micro-RNA and cell-free plasma DNA

Micro-RNAs (miRNAs) are short, non-coding RNAs that by base-pairing with messenger-RNA (mRNA), suppress gene expression and affect a wide range of physiological processes [149]. Some miRNA have a high degree of tissue specificity and are released into the blood after ischemic brain damage [150], liver disease [151], and AMI [152] making them suitable as biomarkers in disease. In

cardiac arrest, a few recent studies have investigated different organ specific miRNAs. A good correlation to long-term outcome was found for the brain specific miRNA-124 [128]. A problem with miRNA is the relatively complicated analysis method that has to be simplified before it can be used as clinical routine.

Cell-free plasma DNA is believed to be released into the circulation after cell death through necrosis or apoptosis, although all aspects of its origin and clearance are not fully understood. Quantification of cell-free plasma DNA was done in a recent publication where an increased level in patients with poor outcome was found [153].

Intensive care of the cardiac arrest patient

The general management of post-cardiac arrest patients should follow the standards of care for other critically ill patients in the ICU setting. Very few large RCTs have been conducted regarding optimal hemodynamic targets, choice of circulatory support, and ventilator strategies and basically the recommendations rely on studies done in other diseases such as sepsis [154] and ARDS [155] with some modifications [5]. Therapies more specific to cardiac arrest patients are discussed further below.

Target temperature management

In 2002 two studies were published comparing hypothermia at 33°C for 12-24 hours with no temperature control and both showed increased survival at 33°C [8, 9]. As a consequence, hypothermia was recommended in an ILCOR advisory statement (2003) and eventually in ERC and AHA guidelines (2005 & 2010) [5, 60]. Prior to these studies animal research had shown positive effects on neurological function, most pronounced if hypothermia treatment was commenced before the ischemic insult [156], but post-ischemic hypothermia induction was also associated with a protective effect [157, 158] and some studies showed a marked effect with virtually abolished neuronal death [159]. Furthermore, longer periods of post-ischemic hypothermia (48 vs. 24 hours) further attenuated the neurological damage [160, 161].

In neonates no less than 11 RCTs has been published as to the effect of mild hypothermia on outcome after hypoxic ischemic encephalopathy. A Cochrane review recently concludes, based on these studies, that cooling to 33°C is safe and improves outcome in term or late preterm newborns with a number needed to treat of approximately 7 to save one life [162].

In adults, a systematic review by Nielsen and co-workers in 2009 showed that time to initiation of induced hypothermia and time to reach target temperature had no significant association to outcome [163]. In 2013 the Target Temperature Management after Out-of-hospital Cardiac Arrest trial (TTM-trial) was published comparing an intervention of 33°C to 36°C for 24 hours in 950 patients with no difference in mortality at the end of trial or neurological function at 180 days [10]. The results from this publication are now being discussed in the research community and the conclusions being drawn are deviating. Some centres emphasize that the results show that 33°C is not harmful as compared to 36°C so they continue treating their patients at 33°C strengthened by previous research, animal studies, and results in neonates. Other centres argue differently and treat their patients at 36°C since 33°C is not proven better and because adverse events may be higher at 33°C with increased duration of sedation, more electrolyte abnormalities, hyperglycemia, coagulopathy, and possibly an increased rate of infections. A statement from the ILCOR was released recently allowing clinicians to treat comatose cardiac arrest patients at 36°C [164]. Importantly, all 36 sites in 10 countries who participated in the TTM-trial have already changed to a target temperature of 36°C.

All are in agreement that temperature control after cardiac arrest should not be abolished. The evidence is, however, limited and emanate from the RCTs in 2002 and observational studies showing association of febrile temperatures to poor outcome [8-10, 108].

Optimal target temperature for the heart

Animal studies

In normal animal hearts, a target temperature of 33°C improved cardiac output and reduced oxygen consumption at the same time as the heart rate was reduced [165-167]. When pacing was done to abolish the bradycardia, the effect of the diastolic dysfunction was more evident which in turn reduced the cardiac index [168].

In failing pig's hearts, mild therapeutic hypothermia as opposed to normothermia improved stroke volume and MAP while reducing heart rate [169]. Although a neutral effect was seen on cardiac output the net effect was positive since central venous saturation, pH and lactate were improved.

In animals after cardiac arrest, Schwarzl and co-workers found improved systolic function and a favourable effect on the systemic oxygen supply-demand balance when comparing hemodynamics in pigs at 33°C and 38°C (normothermia) [170]. There is also evidence of reduced histological myocardial injury and reduced apoptosis in pigs treated with therapeutic hypothermia as compared to normothermia [171].

Human studies

Several small case series have reported beneficial effects of hypothermia on cardiac function and hemodynamic end-points in patients with cardiogenic shock [172-174], other studies show increased in-vitro contractility of muscle fibres from both normal [167] and failing human hearts [11], and in subgroups a reduced infarct size following successful percutaneous coronary intervention (PCI) if hypothermia was administered prior to reperfusion [175]. The COOL shock study I and II demonstrated a variable optimal target temperature in mostly cardiogenic shock patients in-between 32.9-35.0°C and an optimal target temperature could be determined for best cardiovascular performance in each individual patient [173].

Diastolic dysfunction is commonly reported as a negative consequence of a target temperature of 33°C [166, 170, 176]. The reduced heart rate, commonly observed during hypothermia, is thought to oppose the negative effect of reduced left ventricular relaxation.

Randomized controlled trials

Only one quasi-randomised trial compares 33°C to no temperature control and this study excluded patients in shock, defined as a systolic blood pressure below 90 mm Hg despite adrenaline infusion [8]. A subset of patients had a pulmonary artery catheter introduced that showed a lower cardiac index and lower pH in the 33°C group, but no difference in lactate levels.

Current recommendations

Present guidelines do not make any explicit recommendations for patients in shock [68], since shock was an exclusion criterion in previous randomized trials [8, 9]. Several observational studies, however, have reported the safe use of hypothermia in cardiac arrest patients with shock [11-15]. Some of these studies described positive effects with increased MAP [13] and reduced vasopressor requirement [11, 14], while others were more neutral as to the effect of different target temperatures [12, 15].

Post cardiac arrest myocardial dysfunction and shock

Post cardiac arrest myocardial dysfunction (PRMD) is a frequent complication in as much as 68% of cardiac arrest patients and worsens the hemodynamic status and can be lethal [177]. It was initially described by Negovsky as a mixed shock with cardiogenic and vascular components and was normally reversible within 48-72 hours [178]. PRMD can be considered as myocardial stunning although coronary occlusions are not always present. More severe forms of PRMD are seen when primary cardiac cause is the aetiology if the arrest [179], there is long time to ROSC [110], more defibrillations [180], and

higher adrenalin doses used [181]. Furthermore, PRMD is more common in patients with past history of hypertension and old myocardial infarctions [181].

Given the similarities to sepsis, some recommend the use of early goal directed therapy with early volume optimization and if necessary inotropic and/or vasoactive support [154]. To detect PRMD, early echocardiography is recommended in all cardiac arrest patients. Early CAG has been effective in reducing mortality in non-cardiac arrest patients with cardiogenic shock [182], but no studies have been performed in the cardiac arrest setting. Dobutamine is regarded as first-line inotrope in the optimal dose of 5 µg/kg/min when tested in pigs [111, 183]. The use of intra-aortic balloon pump (IABP) in cardiogenic shock, where 40% were recruited from PRMD, showed recently no mortality benefit [184]. If there is a reasonable hope for good neurological outcome in patients with refractory PRMD, some consider minimally invasive left ventricular assistance devices and extracorporeal life support indicated in selected patients and some feasibility studies have been done with good results [185].

Acute coronary syndromes

In acute coronary syndromes without cardiac arrest, an immediate CAG with intervention is correlated to increased survival and less risk of reinfarction [186, 187]. Normal presentations of AMI such as chest pain and ST-elevations on the ECG are difficult to asses in post-cardiac arrest patients and are thus poor predictors of acute coronary occlusion [188]. Also, cardiac biomarkers perform poorly in this setting [129, 130]. Angiographic signs comparable to AMI with recent occlusions or irregular lesions varied from 36 to 69% in a metaanalysis of patients resuscitated from sudden OHCA with no obvious extracardiac cause [189]. Several investigations have reported reduced mortality and improved long-term outcome with early percutaneous coronary interventions (PCIs) regardless of postresuscitation ECG findings [188-191].

In cardiac arrest patients without ST-elevation on postresuscitation ECG Spaulding and co-workers reported culprit coronary lesions in as much as 39% of patients and these findings have been confirmed by others [188, 190]. Furthermore, early CAG increased survival at hospital discharge [192].

The drawback of early CAG is the risk of acute kidney injury from contrast iodine in a critically ill population. Also, some hesitate to use such invasive strategies in patients with potentially poor prognosis and because of lack of RCTs supporting this strategy. Nevertheless, present guidelines from the ERC and recent reviews recommend early immediate CAG and subsequent PCI if indicated, regardless of initial symptoms and/or ECG findings in post cardiac arrest patients [193, 194].

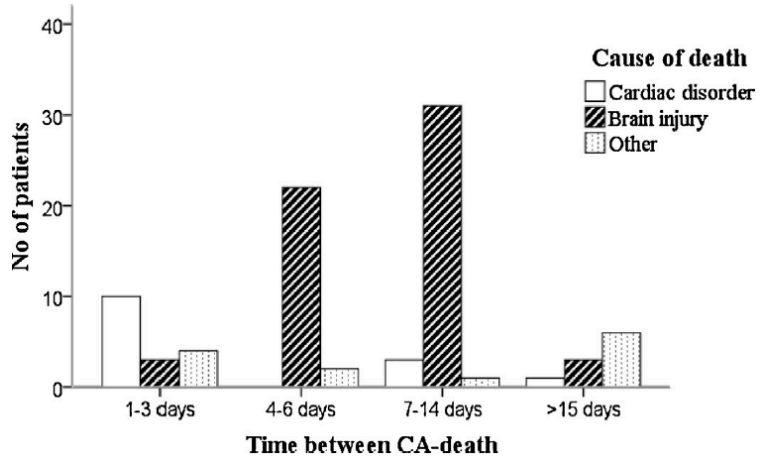
Prognostication

Approximately 50% of patients admitted to the ICU survive in the Scandinavian countries [6, 7]. The incidence of good outcome varies, but most studies conclude that more than 70% are discharged with a CPC 1-2, although commonly with mild cognitive impairment if investigated [2, 7, 195].

The cause of death following cardiac arrest is essential information when attempting to accurately prognosticate outcome. Brain injury is the most frequent cause, accounting for 55-70% of all deaths following cardiac arrest [10, 88, 89, 105]. Cardiac cause of deaths and multiple organ failure are the causes for the majority of the remaining deaths. The distinction of these entities can be difficult in the clinical setting and they may be merged into post-cardiac arrest shock as cause of death [105].

Knowledge of the time of death after cardiac arrest is also important when attempting to prognosticate outcome. In cardiac arrest, the majority of patients that die from cardiac cause do so during the first 1-3 days (Figure 5). So, when prognostication in comatose cardiac arrest patients is attempted 72 hours after normothermia, as recommended in the Swedish guidelines [196], most of these patients do not have to be included in the algorithm.

Figure 5. Cause of death in relation to time from cardiac arrest.



From 'The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest' by Dragancea I, et al. Resuscitation 2013: 84;337-342 © Elsevier Ireland Ltd. Reprinted with permission.

The outcome measure normally used in cardiac arrest research is mortality or neurologic outcome. Neurologic outcome is most often reported using the Cerebral

Performance Category (CPC) scale (Table 1), where a CPC of 1-2 is considered a good outcome and a CPC 3-5 a poor outcome. Patients with CPC 1-2 can at worst have a moderate disability but independently manage activities of daily living [197].

Table 1. Cerebral Performance Categories scale

CPC 1.	Good cerebral performance: conscious, alert, able to work, might have a mild neurologic or psychologic deficit.
CPC 2	Moderate cerebral deficit: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environments.
CPC 3	Severe cerebral deficit: conscious, dependent on others for daily support because of brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4	Coma or vegetative state: any degree of come without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5	Brain death: apenea, areflexia, EEG silence, etc.

Adopted from Safar P. Resuscitation after brain ischemia, in Grenvik A and Safar P Eds: Brain failure and resuscitation. Churchill Livingstone, New York, 1981; 155-184.

Finally, a 'self-fulfilling prophecy' might be an issue when evaluating the effect of prognostication tools. For example, if intensive care is withdrawn due to the results of missing N20 cortical potentials in the somatosensory evoked potentials (SSEP) and death ensues, then no false positives can be identified. Thus, we might falsely award a test for being 100 % specific for poor outcome (death) when in fact, death is a result of our withdrawing of active care based on that prognostication tool.

Demographics and background information

Advanced age, unwitnessed arrest, unshockable rhythm as first monitored rhythm, long time to CPR, and long time to ROSC are all strongly associated with poor neurological outcome but they are not strong enough to be reliable predictors of outcome [66, 85, 195, 198-200].

Clinical examination

Initially after ROSC, many patients have a complete loss of brain stem reflexes. These are then gradually recovered to varying extent during the following days in an orderly fashion in most patients. First brain stem functions recovers,

followed by deeper structures of the brain and finally by cortical activity and consciousness [201].

Clinical examination is based on the determination of coma depth, testing of brain-stem reflexes, and observation of seizures and spontaneous movements. Previously, lack of motor response or an extensor response to pain stimulation day 3 after cardiac arrest were considered acceptable for prognosticating poor outcome, but recent investigations have reported a high rate of false positives [202]. Bilateral losses of pupillary and corneal reflexes are better indices but there are reports of falls positives [202]. The reason for the lack of accuracy of these clinical tests after the introduction of hypothermia is unknown but might be related to lingering effects of sedatives and many centres today advocate prognostication no earlier than at 72 hours after normothermia [16-18].

A generalised, myoclonic state (both face and limbs) during the first day is an ominous sign of poor prognosis although a few reports of successful recovery exist [203, 204].

Neurophysiology

EEG is routinely used in cardiac arrest to diagnose a status epilepticus or to examine cortical activity in prognostication of outcome in still comatose patients after cardiac arrest. EEG is affected by sedation but not by hypothermia. EEG has limited value as a single test for prognostication but some patterns, such as flat or suppression-burst [205] and nonreactive EEG response [206] is indicative of poor prognosis, especially if performed late. The drawbacks are that EEG is a snapshot of 20-30 minutes of cortical activity and can thus not assess trends if not repeated frequently [16].

The continuous EEG (cEEG) monitoring offers the advantage of allowing for trend analysis. It may be presented as a simplified, bilateral EEG of raw data in combination with an amplitude-integrated presentation (aEEG). cEEG is initiated by ICU nurses and registration is begun immediately after admittance to the ICU providing a possibility to assess trends, evolution of EEG patterns and to detect a nonconvulsive electrographic status epilepticus. Dichotomization of patterns into continuous vs. non-continuous (suppression-burst, low-voltage, and electrographic status) patterns can be used in prognostication with good accuracy [207, 208].

SSEP is one of the most solid investigations used in prognostication and has the advantage of being insensitive to sedatives. When used before the introduction of hypothermia it was considered to have no false positives [119]. Recent reports, however, challenge this [209] and SSEP has to be evaluated in combination with other prognostic tools by using a multimodal strategy [210, 211]. Also, the sensitivity to predict poor outcome is low (<50%) and it is not available in all hospitals.

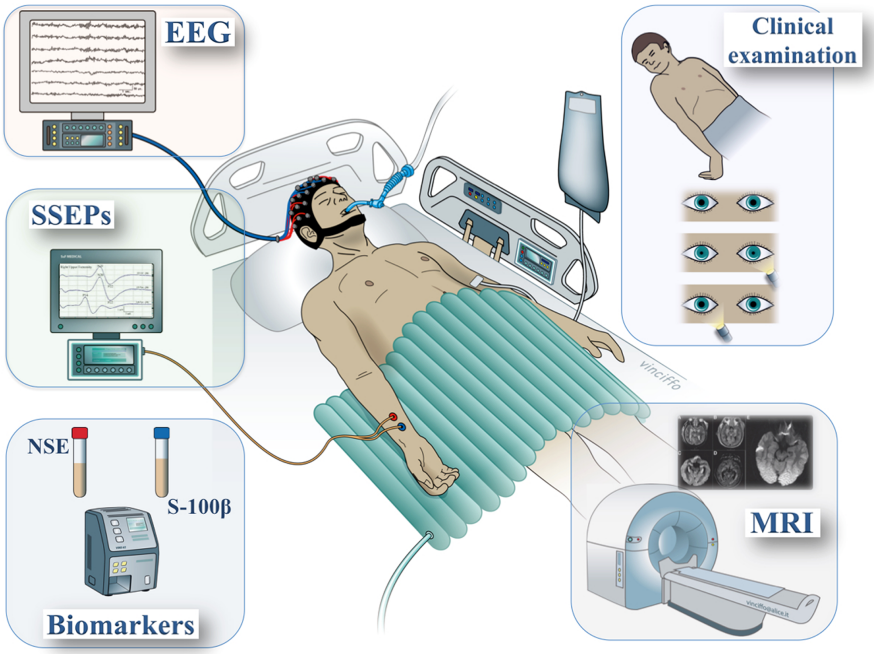
Imaging

An early CT of the brain is often used to exclude any unexpected cause of intracerebral coma in still comatose patients after cardiac arrest. Also, some studies report signs of oedema on the initial CT examination to be an early predictor of poor neurological outcome but further research is needed [212]. MRI can be used as a prognostic method visualising post-anoxic brain injury at 2-5 days following cardiac arrest [213]. A normal MRI scan can in selected comatose patients be indicative of prolonged observation and active treatment [16].

Biomarkers

There have been many studies of biomarkers to prognosticate outcome in cardiac arrest. Most of these are hampered by significant overlap between outcome groups limiting their use in clinical practice. NSE is the most adopted biomarker and used in many centres after cardiac arrest.

Figure 6. Multimodal approach to asses prognosis in comatose survivors after cardiac arrest treated with targeted temperature management.



From 'How to asses prognosis after cardiac arrest and therapeutic hypothermia' by Taccone FS, et al. Critical Care 2014: 18;202 © 2014 BioMed Central Ltd. Reprinted with permission.

Specific cut-off levels for poor outcome have to be used cautiously and adapted to the current assays used at the centre. Low NSE concentrations in still comatose cardiac arrest patients should alert the clinician that a potentially treatable condition might exist [16].

Other biomarkers, such as PCT or CT-proAVP, assessing inflammation or stress, have the advantage of having their best predictive power already at admission to the ICU potentially providing the clinician with an earlier indication of outcome [115-118]. Since the cause of death is not uniform in cardiac arrest patients, it is evident that if biomarkers should be accurate predictors of outcome, they have to be combined and probably used in conjunction with other prognostic modalities in a multimodal approach (Figure 6).

Aims of the thesis

i. To investigate the release profiles of CT-proAVP (copeptin), MR-proANP, prx4, PCT, and CRP in patients treated with mild induced hypothermia after cardiac arrest, and study their association to the PCAS and long-term outcome.

ii. To investigate if PCT and CRP are associated to early infection and/or the PCAS.

iii. To investigate if the addition of another biomarker to NSE can facilitate prognostication in patients treated with mild induced hypothermia after cardiac arrest.

iv. To investigate the effects of two target temperatures (33°C and 36°C) on hemodynamics and vasopressor requirement in post-reuscitation cardiac arrest patients.

v. To investigate the association of two target temperatures (33°C and 36°C) to outcome and severity of shock in post-resuscitation cardiac arrest patients with shock on admission.

Methods

The materials and methods are described in detail in each paper (see attachments).

Paper I, II, and V

Objective

Paper I:

To investigate serial serum concentrations of PCT and CRP in patients treated with mild hypothermia after cardiac arrest, and to study their association to severe infections, the PCAS and long-term outcome.

Paper II:

To investigate serial serum concentrations of the stress hormone CT-proAVP (copeptin), the cardiac biomarker MR-proANP and a biomarker of oxidation injury, peroxiredoxin 4 (Prx4) in patients treated with mild hypothermia after cardiac arrest, and study their association to the PCAS and long-term outcome.

Paper V:

To investigate if the brain biomarker NSE in combination with a biomarker for stress; CT-proAVP (copeptin), oxidation; Prx4, inflammation; PCT, or with biomarkers from the heart; MR-proANP or TnT can improve the prognostic accuracy of long-term outcome after OHCA. This is a hypothesis generating pilot study to be further investigated in the larger TTM-trial cohort [10].

Ethics

Studies I, II and V were approved by the Regional Ethical Review Board at Lund University (decisions 411/2004 and 223/2008), and informed consent was sought from next of kin or, retrospectively, from the patient.

Patients

Paper I and II:

Eighty-four comatose patients resuscitated from in-hospital or out-of-hospital cardiac arrest (≥18 years) at Lund University hospital between June 2003 and January 2007, regardless of initial rhythm, with sustained unconsciousness (GCS ≤ 7) after ROSC, were included.

Paper V:

Sixty-two of the 84 patients above with OHCA with a presumed cardiac cause were included, excluding unwitnessed asystole as first monitored rhythm. This selection of patients was done to unify the cohort and align it with the inclusion criteria for the TTM-trial [10].

Methods

All patients were treated with mild induced hypothermia at 33±1°C for 24 hours using external (CritiCool, TREM, Israel or Arctic Sun, Medivance, CO, USA) or internal (Icy Cath, Alsius, CA, USA) cooling. Induction was accomplished through saline intravenously (20-30 ml/kg given over 10-20 minutes) accompanied by surface cooling with alcohol wipes and ice packs at the attending physician's discretion. Rewarming was active and controlled using devices at 0.5°C per hour. Major exclusion criteria were terminal disease, intracerebral haemorrhage, pregnancy or major trauma.

Patients were sedated with midazolam and fentanyl and shivering was treated with rocuronium at the attending ICU physician's discretion. The sedation was stopped at normothermia if possible and otherwise kept to a minimum to facilitate continued intensive care until extubation. The protocol targeted a MAP > 65 mm Hg and the use of vasoconstrictors, inotropes and IABP support when indicated. No routine CAG were required in the protocol.

At 72 hours following normothermia neurological evaluation was performed including anamnestic information, clinical neurologic examination, EEG, SSEP, and MRI. If the patient had a GCS-motor status of 1-2 or bilateral loss of N20 peak on the SSEP, intensive care was withdrawn. If the neurologic evaluation was inconclusive, the observation period was prolonged.

Biomarker analysis

Serum samples from arrest patients treated with mild hypothermia were collected serially; at admission, 2, 6, 12, 24, 36, 48 and 72 hours after cardiac

arrest. PCT, CT-proAVP, MR-proANP, Prx4 and CRP were measured at all of these time points, while TnT and NSE were measured at 12, 24, and 48 hours after cardiac arrest.

Samples for measurements of PCT, CT-proAVP, MR-proANP, and Prx4 were centrifuged and frozen (-70°C) immediately after collection. After the end of the study, samples were thawed once, centrifuged at 4000 rpm for five minutes, aliquoted, and refrozen (-70°C) for later analysis by BRAHMS Aktiengesellschaft, Hennigsdorf, Germany. During aliquoting, the samples were kept on ice. Samples for measurements of TnT, NSE and CRP were measured at the Lund University hospital, Department of clinical chemistry core laboratory.

Paper I:

PCT assay: Analyses were performed using an ultrasensitive immune-luminometric assay (BRAHMS PCT sensitive LIA; BRAHMS Aktiengesellschaft, Hennigsdorf, Germany). The assay had a functional sensitivity at 7 pg/mL (which is below the median of the normal range) and an interassay coefficient of variation of 8% at 30 *p*g/mL.

CRP assay: Analyses were performed using quantitative immunological determination of CRP (Cobas, Roche Diagnostics, Mannheim, Germany). The assay had a functional sensitivity at 0.3 mg/dl and an interassay coefficient of variation of 5% at 65 mg/mL.

Paper II:

CT-proAVP assay: Measurement of CT-proAVP was performed with a commercial sandwich immunoluminometric assay (BRAHMS. CT-proAVP LIA, Thermo Scientific Biomarkers, Hennigsdorf, Germany), as described in detail elsewhere [140]. Since this initial publication, the assay was modified as follows: The capture antibody was replaced by a murine monoclonal antibody directed to amino acids 137 to 144 (GPAGAL) of provasopressin. The lower detection limit was 0.4 *p*mol/L, and the functional assay sensitivity (<20% inter-assay coefficient of variance) was less than 1 *p*mol/L.

MR-proANP assay: MR-proANP was measured with an automated sandwich chemiluminescence immunoassay on the KRYPTOR System (Thermo Scientific Biomarkers, Hennigsdorf, Germany). The assay is based on the sandwich chemiluminescence assay, which is described in detail elsewhere [214]. Performance of MR-proANP included a limit of quantitation of 4.5 *p*mol/L, within-run imprecision coefficient of variation of 1.2% and total imprecision of 5.4%. The lower detection limit was 2.1 *p*mol/L, and the functional assay sensitivity (<20% inter-assay coefficient of variance) was 10 *p*mol/L.

Prx4 assay: Prx4 serum levels were measured in a blinded batch analysis using a newly developed two-step sandwich immunoluminometric assay [215]. The assay applies two monoclonal mouse-antibodies to amino acids 39-51 of

human Prx4. In brief, 100 µl of patient samples or standards were incubated in duplicate with 100 µl of sample buffer in antibody-coated tubes for 20 hours under agitation at room temperature. Tubes were washed four times with and subsequently incubated with 100 µl of acridinium ester-labelled tracer antibody for 2 hours under agitation at room temperature. After four washing steps bound chemiluminescence was measured in a luminometer. The functional assay sensitivity (interassay coefficient of variation <20 %) is 0.51 arb. U/L and the lower detection limit is 0.34 arb. U/L.

Paper V:

NSE assay: Samples were centrifuged and kept refrigerated if analysed within 24 hours, otherwise they were frozen (-20°C) and analysed within 7 days. The NSE analysis was performed using LIAISON® NSE (DiaSorin AB, Sundbyberg, Sweden), detection limit 0.04 µg/L, reference interval < 12.5 µg/L. Samples with visible haemolysis were discarded.

TnT assay: Serum samples were collected and transferred to the clinical chemistry laboratory at the participating hospital and analysed (Cobas, Roche Diagnostics, Mannheim, Germany). Detection limit 0.01 µg/L, reference interval 0.03-25 µg/L.

PCT, CT-proAVP, MR-proANP, and Prx4 were analysed in separate aliquots as stated above.

We chose to group the possible combinations of NSE into an early group including samples at 12 hours, an intermediate group including samples at 24 hours, a late group including samples at 48 hours and a mixed early and late group, combining NSE at 48 hours with an early biomarker (12 hours).

Outcome

Long-term outcome was assessed using the CPC scale at 6 months where a CPC of 1-2 is considered a good outcome and a CPC 3-5 a poor outcome (Table 1). An occupational therapist and, when indicated, a neurologist performed the evaluations.

Surrogate markers for the PCAS in paper I and II were considered to be time to ROSC and the cardiovascular part of the Sequential organ failure assessment score (SOFA-score). The cardiovascular-SOFA score was subdivided into three groups; SOFA 0-1 as group 1, SOFA 2-3 as 2 and SOFA 4 as 3.

The presence of infection in patients in paper I was evaluated with three different definitions of infection. First, a modified, simplified Clinical Pulmonary Infection Score (CPIS) classified patients as having a pneumonia on the basis of new pulmonary infiltrates plus at least three of the following criteria: Body temperature >38°C or instituted treatment against hyperthermia or temperature

<36°C more than 24 hours after end of rewarming, white blood cell count ≥ 10000/mm^3 or ≤ 4000/mm^3, purulent aspect of tracheal aspirates, positive semi-quantitative culture from tracheal aspirates and poor oxygenation (PaO_2/FiO_2 < 32 kPa) [216]. Second, the extended definition of infection classified patients as infected when there was clinical evidence of infection and patients received antibiotics by the treating physician (with or without documented positive bacterial cultures) [137]. For the first two definitions, data was collected retrospectively from our ICU's clinical information system during the first five days of care. Third, the International Cardiac Arrest Registry (INTCAR) defined pneumonia with four requirements: new or progressive consolidation on the chest radiograph, fever, leukocytosis, and the presence of purulent tracheobronchial secretions. It encompasses the entire ICU stay and was recorded prospectively [217].

Paper III and IV

Objective

Paper III:

To investigate if a targeted temperature at 33°C as compared to 36°C would increase survival and reduce the severity of circulatory shock in patients with shock on admission after OHCA.

Paper IV:

To investigate the hemodynamic profiles associated with different target temperatures and to assess the prognostic implication of inotropic/vasopressor support and MAP after OHCA.

Ethics

Ethics committees in each participating country approved the trial.
Informed consent was obtained or waived according to national regulations, and guidelines for Good Clinical Practice were followed and monitored.

Patients

Paper III:

One-hundred and thirty-nine adult patients (≥18 years) resuscitated from OHCA of presumed cardiac cause, irrespective of the initial rhythm, who remained unconscious (Glasgow coma scale <8) after sustained (>20 minutes) ROSC that had moderate shock on admission had been randomly assigned to a targeted temperature management at 33°C (n=71) or 36°C (n=68).

Moderate shock was defined as a systolic blood pressure below 90 mm Hg for more than 30 minutes, or the need of supportive measures (fluid loading, vasopressors, inotropic medication, and/or intra aortic balloon pump) to maintain a blood pressure ≥ 90 mm Hg, and/or end-organ hypoperfusion (cool extremities, urine output of less than 30 ml per hour). This cohort of shock patients was a predefined subgroup in the TTM-trial including 950 patients [10].

Main exclusion criteria were unwitnessed arrest with asystole as primary rhythm, an interval from ROSC to screening of more than 240 minutes, and a severe shock state (defined as a systolic blood pressure below 80 mm Hg in spite

of fluid loading, vasopressors, inotropes, and/or treatment with intra-aortic balloon pump) that could not be reversed within the inclusion time window.

Paper IV:

Nine-hundred and twenty patients (97%) with available vasopressor data out of 950 patients from the TTM-trial, randomised to a targeted temperature management at 33°C or 36°C [10].

The patients were dichotomised into patients with a high vasopressor requirement, defined by a cardiovascular-SOFA score of 4 (n=456), and a low vasopressor requirement, defined by a cardiovascular-SOFA score ≤ 3 (n=464).

Protocol

Patients had been randomized 1:1 to a target temperature of 33°C or 36°C for 24 hours. The intervention period of 36 hours commenced at the time of randomization. All patients were intubated, mechanically ventilated and sedated until the end of the intervention period or longer when indicated. The goal was to achieve the assigned temperature as rapidly as possible with ice-cold fluids, ice packs, and intravascular or surface temperature management devices at the discretion of each site. After 28 hours, gradual rewarming to 37°C with a maximum speed of 0.5°C per hour was commenced in both groups. At 36 hours, mandatory sedation was discontinued or tapered. After the intervention period, the intention was to maintain the body temperature for unconscious patients below 37.5°C until 72 hours after the cardiac arrest [10].
Fluid administration was given at the discretion of the treating physician at each site, guided by standard procedures for hemodynamic support. No pre-specified targets of blood pressure, heart rate or urinary output were given due to the pragmatic study design [10]. Heart rate, MAP, lactate, and central venous oxygen saturation ($S_{cv}O_2$) were measured at specific time points; admission, 0 (time of randomization and start of intervention), 4, 12, 20, 28, 32, and 36 hours. In the ICU, fluid balance, urine output, peak lactate and need of vasopressors and/or inotropes were recorded for the first 7 days.

Vasopressor requirements were recorded as the cardiovascular sub-score of the SOFA-score and further extended with information regarding requirements of vasopressors above a SOFA-score of 4 in four further increments (5-8): 0) MAP ≥70 mm Hg, 1) MAP <70 mm Hg, 2) any dose of dobutamine or dopamine ≤ 5 µg/kg/min, 3) dopamine 5-15 µg/kg/min or epinephrine/norepinephrine ≤0.10 µg/kg/min, 4) dopamine >15 µg/kg/min or epinephrine/norepinephrine >0.10 µg/kg/min, 5) epinephrine/norepinephrine ≥0.25 µg/kg/min, 6) epinephrine/norepinephrine ≥0.50 µg/kg/min, 7) epinephrine/norepinephrine ≥0.75 µg/kg/min, and 8) epinephrine/norepinephrine >1 µg/kg/min [218].

Paper III used the cardiovascular-SOFA score 0-8 as presented above to stratify patients with increasing vasopressor requirements. Paper IV used the cardiovascular-SOFA score 0-4 and dichotomised patients into; high vasopressor requirement, defined by a cardiovascular-SOFA score of 4 (n=456) and a low vasopressor requirement, defined by a cardiovascular SOFA score ≤ 3 (n=464).

Outcome

Paper III:

Primary outcome was 180-day mortality. Secondary outcomes were ICU-mortality, 30-day mortality, severity of shock assessed by heart rate, MAP and lactate during the intervention (0-36 hours), and daily peak lactate, fluid balance and extended cardiovascular SOFA-score during the first 7 days.

Paper IV:

Primary outcome was 30-day mortality. Secondary outcomes were the effect of targeted temperature on heart rate, MAP, serum lactate, and $S_{cv}O_2$.

Results

The results are described in detail in each paper (see attachments).

Paper I

PCT and CRP release patterns

The release curves for PCT and CRP are presented in figure 7. PCT displayed an earlier release pattern than CRP with a significant increase within 2 hours, increasing further at 6 hours and onwards in patients with poor outcome (Figure 7 a). CRP increased later and continued to rise during the study period (Figure 7 b). There were significant differences in concentrations between the good and poor outcome groups at all time points for PCT and only at 24 hours for CRP.

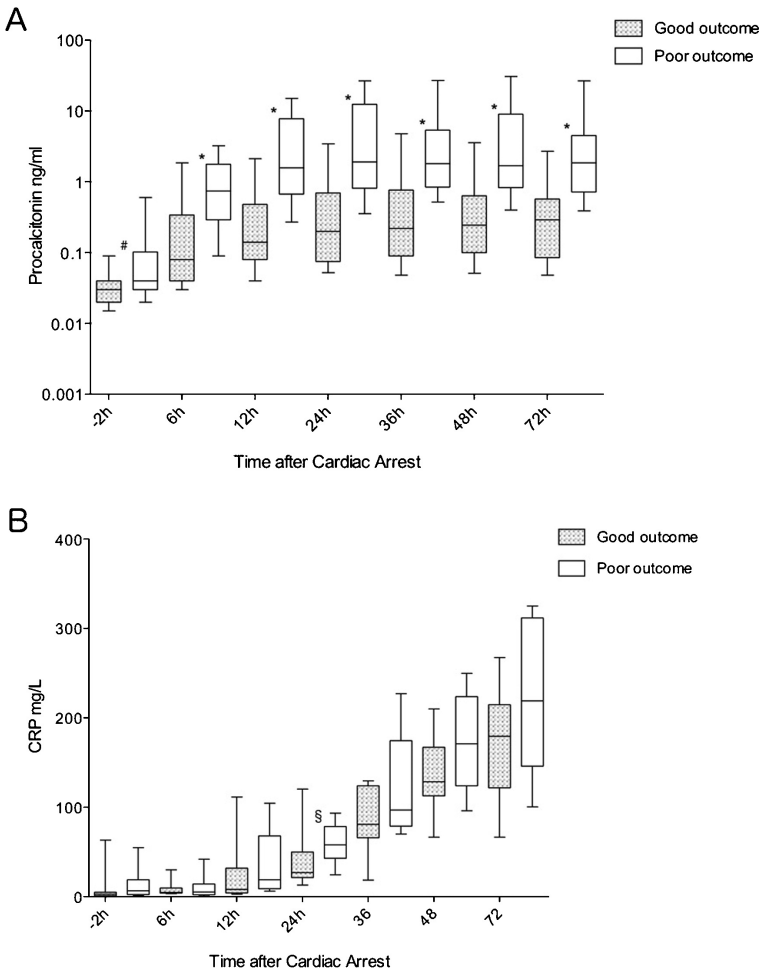
Accuracy for predicting poor outcome

ROC analyses showed high potential for PCT to predict poor neurological outcome with an AUC of 0.88 at 12 hours, 0.86 at 24 hours and 0.87 at 48 hours. The corresponding AUC values for CRP were 0.68 at 12 hours, 0.75 at 24 hours and 0.66 at 48 hours. Using a cut off value for PCT of 0.5 ng/mL, a suggested discriminator between local and systemic response [219], at 12, 24 and 48 hours provided a positive predictive value (PPV) for poor outcome of 0.78 (95% CI 0.63-0.89) and a negative predictive value (NPV) of 0.83 (95% CI 0.67-0.93) at 12 hours. To achieve 100% specificity for a poor outcome at 12 hours, the cut-off value needed to be set at 10 ng/mL at 12 with a resulting sensitivity of 15%.

Correlation of PCT and CRP to infection

Patients with infection according to the modified, simplified CPIS, extended definition or INTCAR did not have significantly increased PCT concentrations, compared to uninfected patients at any time point.

Figure 7. Release pattern for a) PCT and b) CRP after cardiac arrest in the good and the poor outcome group. The line in the box represent the median, the outer limits of the box represent the inter-quartile range. Outliers are not shown. # $p < 0.05$, § $p < 0.01$ and * $p < 0.001$



Correlation of PCT to the PCAS

The circulation-SOFA score at 24 and 48 hours correlated with increased PCT values but was significantly higher at 48 hours only (Figure 8). PCT at 12, 24 and 48 hours correlated strongly with time to ROSC with a correlation coefficient of 0.64, 0.59 and 0.59, respectively (Figure 9).

Figure 8. Cardiovascular-SOFA score divided into 3 groups, 0-1, 2-3 and 4 versus PCT concentrations at 48 hours. The line in the box represent the median, the outer limits of the box represent the inter-quartile range. Outliers are not shown. * p = 0.004

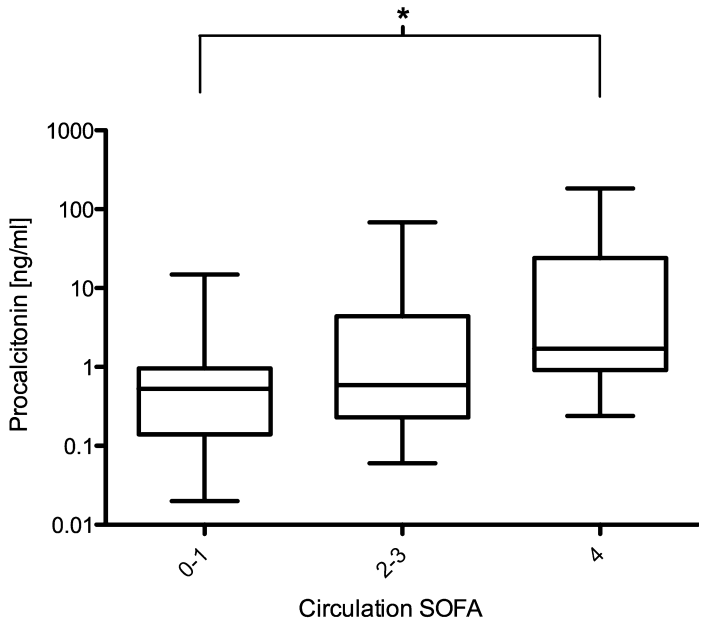
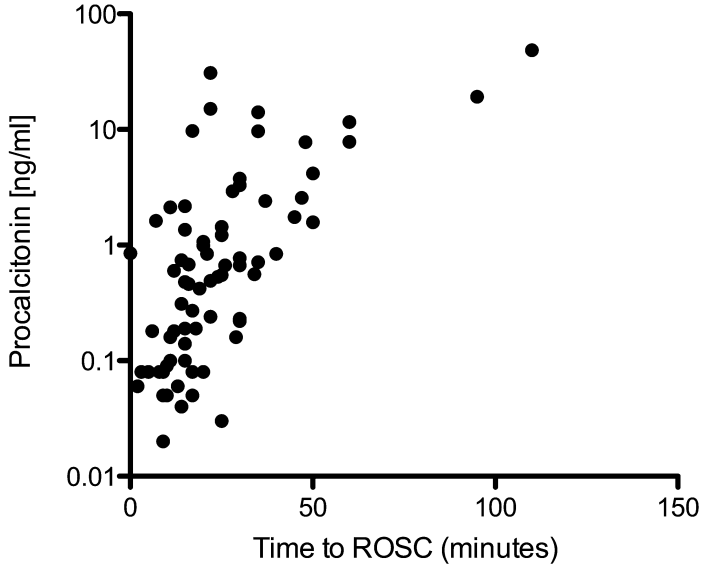


Figure 9. PCT correlated to time to return of spontaneous circulation with a Spearman correlation coefficient of 0.64.



Summary of paper I

Procalcitonin concentrations increase rapidly in mild hypothermia treated patients with poor outcome after resuscitation from cardiac arrest and may serve as an early predictor of poor outcome although no relevant cut-off levels were identified. Furthermore, increasing PCT and CRP concentration during the first 72 hours after cardiac arrest are probably correlated to the severity of the PCAS and not due to early infection.

Paper II

CT-proAVP (copeptin)

The highest concentrations were measured at admission, subsequently falling throughout 72 h (Figure 10 a). There were significant differences between CT-proAVP concentrations in the good and poor outcome groups at all time points from 6 hours to 72 hours (Figure 10 a). ROC-analysis at 12 hours yielded the best discrimination with an AUC of 0.85. A cut-off value of CT-proAVP >35.4 *p*mol/L was chosen from the ROC curve with a resulting in a PPV of 0.77 (95% CI 0.61-0.89) and a NPV) of 0.78 (95% CI 0.62-0.89). Choosing a cut-off value with 100% specificity for poor outcome resulted in a sensitivity of 25.9% (95% CI 13.0-42.1).

Time to death was analysed by Kaplan-Meier survival curves and showed an incremental decrease in survival with increasing CT-proAVP concentrations showing significant discrimination between all quartiles of CT-proAVP concentrations (Fig. 11).

MR-proANP

Serum concentrations of MR-ProANP peaked at admission, falling throughout the period of hypothermia and starting to increase again at 36 hours (Figure 10 b). Significant differences between the good and poor outcome groups were seen from 2 hours to 36 hours (Figure 10 b). ROC analysis at 12 hours after cardiac arrest yielded an AUC of 0.77 and a best cut-off concentration of > 257 *p*mol/L with a corresponding PPV of 0.81 (95% CI 0.63-0.93) and NPV of 0.70 (95% CI 0.55-0.83). Choosing a cut-off value with 100% specificity for poor outcome resulted in a sensitivity of 43.6% (95% CI 27.8-60.4).

Prx4

Serum concentrations of Prx4 decreased from admission to 12 hours and increased thereafter. Significant differences between the good and poor outcome groups were seen from 2 hours to 36 hours (Figure 10 c). ROC analysis at 12

hours yielded a best AUC of 0.76 and a cut-off concentration of >1.71 arb. U/L with a PPV of 0.74 (95% CI 0.50-0.80) and NPV of 0.67 (95% CI 0.57-0.87).

Correlation to the PCAS

CT-proAVP at 2, 6 and 12 hours correlated with time to ROSC with a correlation coefficient of 0.62, 0.63 and 0.57, respectively. Cardiovascular-SOFA score day 2 correlated significantly to CT-proAVP at 24 and 36 hours (p=0.04) and to MR-proANP at 6, 12 and 24 hours (p=0.003, 0.001, and 0.026, respectively).

Summary of paper II

CT-proAVP, MR-proANP, and Prx4 concentrations all increase rapidly in mild hypothermia treated patients and are significantly higher if poor outcome after resuscitation from cardiac arrest. CT-proAVP was the best predictor of outcome in this study, but all tested biomarkers show significant overlap in concentrations between outcome groups hindering relevant cut-off levels for poor outcome to be identified. CT-proAVP and MR-proANP had significant correlation to the PCAS.

Fig 10. Release patterns for a) CT-proAVP (copeptin), b) MR-proANP, and c) Prx4 in the good and poor outcome group. CT-proAVP and MR-proAVP is in *p*mol/L and Prx4 in arbitrary U/L. Note the logarithmic scales for CT-proAVP and Prx4. The line in the box represents the median, the outer limits of the box represent the inter-quartile range. Outliers are not shown. * $p < 0.001$, § $p < 0.01$, and # $p < 0.05$

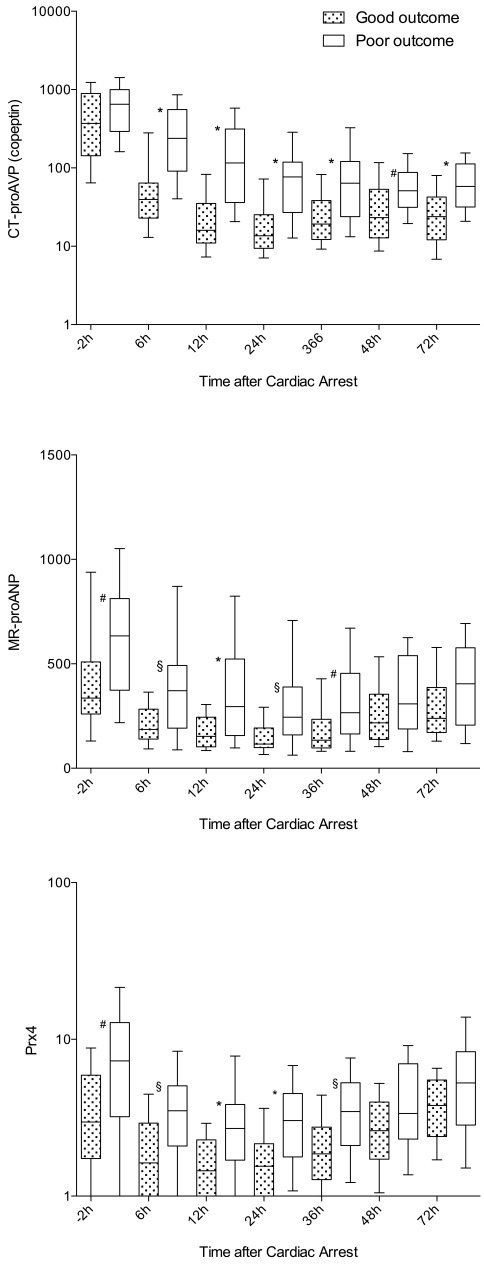
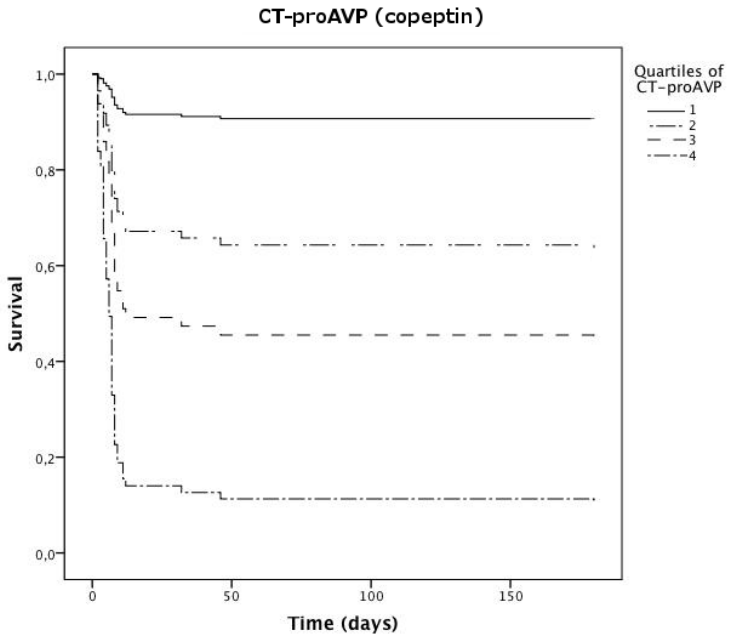


Fig 11. Kaplan Meier survival curves for CT-proAVP (copeptin). The time to death was analysed based on CT-proAVP quartiles. 1st quartile CT-proAVP < 15.0 *p*mol/L, n=20, 2nd quartile CT-proAVP 15.1-35.1 *p*mol/L, n=19, 3rd quartile CT-proAVP 35.2-118.0 *p*mol/L, n=20, 4th quartile CT-proAVP > 118.1 *p*mol/L, n=19. p<0.001 between quartile 1 and 2, 2 and 3, p<0.01 between quartile 3 and 4.



Paper III

Patients in shock vs. patients with no shock on admission

Patients in shock on admission (n=139), irrespective of intervention arm, were older, received more epinephrine during resuscitation, received more often mechanical active compression-decompression devices, had longer time to ROSC, and had a higher serum lactate at admission than patients with no shock (n=798). The increased relative risk of death in patients with shock on admission was 1.51 (95% CI 1.32-1.75, p<0.001) at 180 days.

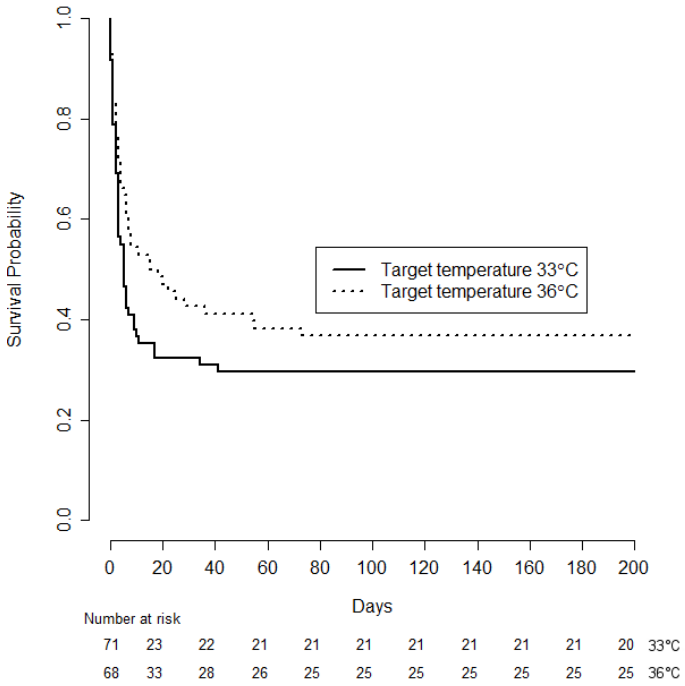
Mortality at 33 and 36°C in patients with shock on admission

Targeted temperature management at 33°C or 36°C did not significantly influence 180-day mortality for patients in moderate shock on admission [log-rank test, p=0.17, hazard ratio 1.33 (95% CI 0.88-1.98)] (Figure 12). ICU mortality and

mortality at 30 and 180 days did not differ between the 33°C and 36°C groups; 61 % (43 of 71 patients) vs. 44 % (30 of 68 patients), p=0.06, 68 % (48 of 71 patients) vs. 57 % (39 of 68 patients), p=0.23, and 70 % (50 of 71 patients) vs. 63 % (43 of 68 patients), p=0.47, respectively.

An adjustment for potential baseline characteristic dissimilarities in the 33°C vs. 36°C groups resulted in a significant difference in ICU mortality between groups in favour of 36°C (p=0.03).

Figure 12. Probability of survival through 180 days. Kaplan-Meier estimates of the probability of survival for patients with shock on admission allocated to either 33°C or 36°C and the number of patients at risk at indicated time points. Log-rank test of the 180-day follow-up period, p=0.17



A multivariate logistic regression of variables associated with 180-day mortality showed that the absence of a shockable rhythm (Odds Ratio 23.1 (95% CI, 2.99-178.6), p=0.003) and longer time to ROSC (OR 1.02 per additional minute (95% CI, 1.002-1.034), p=0.027) were statistically significant predictors of mortality, while previous cardiac disease, successful PCI, age and intervention arm were not (Table 2).

Table 2. Multivariate logistic regression modelling of variables associated with 180-day mortality for patients with shock on admission.

Variable	OR (95% CI)	p-value
Targeted temperature management at 33 °C	1.46 (0.60-3.56)	0.40
Age – per yr	1.04 (0.97-1.09)	0.07
Previous cardiac disease *	1.36 (0.46-3.99)	0.58
Non-shockable rhythm #	23.1 (2.99-178.6)	0.003
Time to ROSC – per min §	1.02 (1.002-1.034)	0.027
Successful PCI	0.43 (0.16-1.14)	0.09

OR denotes odds ratio, CI confidence interval, ROSC return of spontaneous circulation, PCI percutaneous coronary intervention.
* Including previous chronic heart failure, previous myocardial infarction, ischemic heart disease, previous PCI or bypass surgery, and arterial hypertension.
# Asystole or pulseless electrical activity
§ For unwitnessed arrests; intervals were calculated from time of the emergency call

Severity of chock at 33 and 36°C during intervention (0-36 hours)

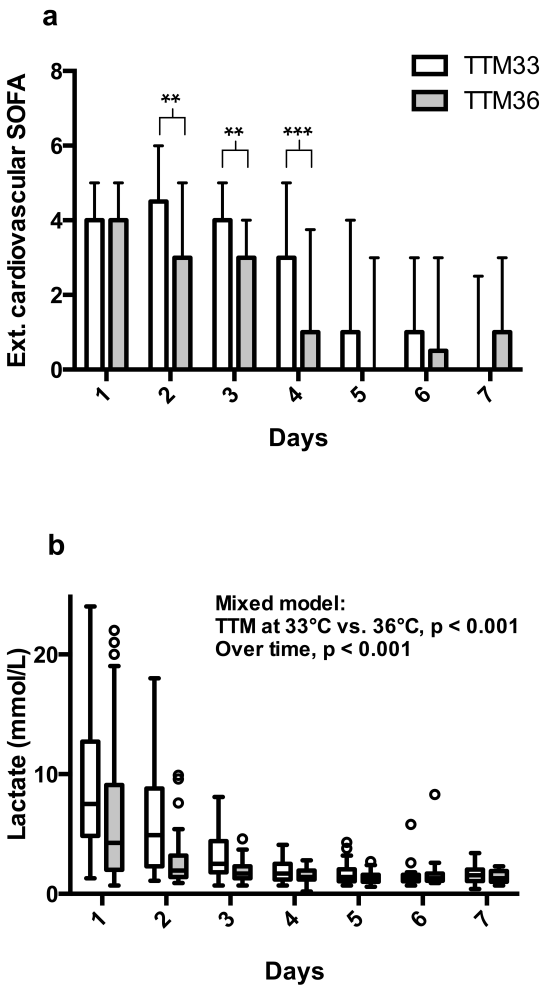
During the intervention period, lactate levels were higher in the 33°C group (mixed model, p=0.004) as compared to the 36°C group, while no significant differences in heart rate or MAP were found.

Severity of chock at 33 and 36°C during the first 7 days

During the first seven days in the ICU, an intervention at 33°C vs. 36°C resulted in increased requirements of vasopressors from day 2 to 4, with higher median extended cardiovascular SOFA-scores of 4.5 vs. 3 ($p<0.01$), 4 vs. 3 ($p<0.01$) and 3 vs. 1 ($p<0.001$), respectively (Figure 13 a).

Using a mixed model from day 1 to 7, there were significant differences in lactate between groups ($p<0.001$) and over time ($p<0.001$) with higher lactate levels in the 33°C group (Figure 13 b). There were no significant differences in daily fluid balances between the 33°C and 36°C group (mixed model, p=0.1).

Figure 13. Extended cardiovascular Sequential Organ Failure Assessment (SOFA)-score (0 to 8, where 0 represents a mean arterial pressure > 70 mm Hg and 8 the highest dose of vasopressor registered) and lactate concentrations for patients with shock on admission during the first seven days of stay in the Intensive Care Unit in the 33°C and 36°C treatment groups. The whiskers of the bars in Figure 6 a represent the upper inter-quartile ranges. The line in the box in Figure 6 b represents the median, the outer limits of the boxes represent the inter-quartile ranges and whiskers the complete range. Outliers are shown as circles. ** $p < 0.01$, *** $p < 0.001$. TTM denotes targeted temperature management



Summary of paper III

In patients with moderate shock on admission after resuscitation from cardiac arrest, there were no benefit of targeted temperature management at 33°C as compared to 36°C. In fact, crude ICU mortality showed a tendency of increase in the 33°C group that became significant after adjustment for potential differences in baseline characteristics. Lactate levels and requirement for vasopressors, which we consider surrogate markers of severity of shock, were higher in the 33°C group, while heart rate and MAP did not differ between groups during the intervention.

There were no significant differences between intervention groups regarding long-term outcome.

Paper IV

Characteristics of patients with high vs. low vasopressor requirement

Patients in the high vasopressor group were older, had longer time to ROSC, fewer had bystander CPR, and shockable rhythm on arrival as compared to the low vasopressor group.

Patients that had a high vasopressor requirement had a significantly higher mortality at 30 days (53%) as compared to the low vasopressor group (34%) (log-rank test, $p<0.0001$). The hazard ratio for 30-day mortality in patients with need for high vasopressor doses during the intervention period was 1.38 (95% CI 1.11-1.71, $p=0.004$) in a multivariable model adjusting for target temperature management group, demographics, pre-hospital factors, and co-morbidities.

The effect of targeted temperature management on the hemodynamic profile

Patients in the 33 and 36°C targeted temperature groups had similar hemodynamic and metabolic characteristics at time of randomization. During the 36-hour intervention period there was no overall difference in MAP in the 33 and 36°C groups with the exception of the rewarming phase where MAP was significantly lower in the 33°C group. Heart rate was significantly lower and lactate levels were significantly higher in the 33°C group throughout the intervention. There was no overall difference in central venous saturation or differences in central venous saturation at any time point in the intervention groups.

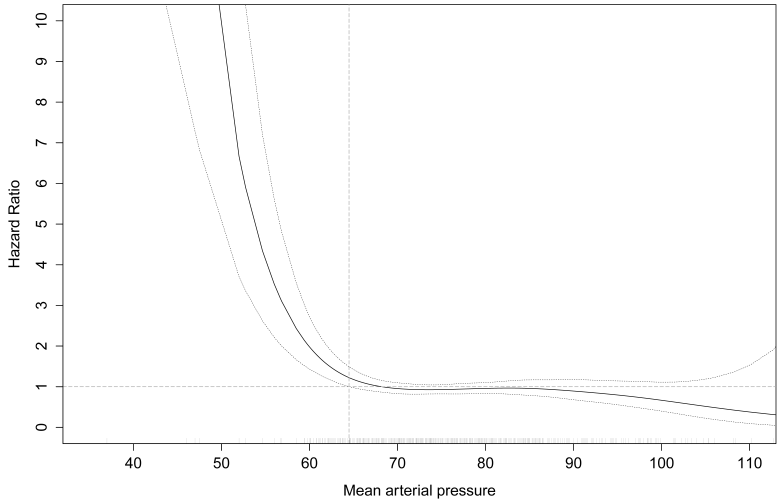
There was a higher prevalence of high vasopressor requirement in the 33°C group (54%) as compared to the 36°C group (45%), $p=0.03$. Furthermore, more patients in the 36°C group did not require any vasopressors during intervention (14% vs. 9%, $p=0.03$).

The effect of MAP on outcome

In a multivariable model (adjusting for targeted temperature group, sex, age, primary rhythm, witnessed arrest, bystander CPR, time to ROSC, vasopressor group, and initial levels of lactate) average MAP during intervention was an independent predictor of 30-day mortality [HR=0.90 (95% CI 0.85-0.95) per 5 mmHg increase, p=0.0008].

A fitted smoothing spline plot from a multivariable Cox-model with average MAP during intervention is shown in figure 14, and suggested that MAP below 65 mm Hg was associated with increased mortality.

Figure 14. Hazard ratio for the average of recorded mean arterial pressure (MAP) values during 36-hours intervention of targeted temperature management. Fitted smoothing spline plot from multivariable Cox model. Hazard ratios with 95% confidence intervals (CI) for 30-day mortality adjusted for temperature allocation group, sex, age, witnessed arrest, bystander cardio-pulmonary resuscitation, initial rhythm, time to ROSC and initial lactate. The vertical line represent the intersection of the lower 95% CI and the harzard ratio of 1. The distribution of sample size across MAP is illustrated with minor ticks along the x-axis.



Summary of paper IV

Patients with a high vasopressor requirement during the intervention period had a worse outcome. Patients allocated to the 33°C group had a higher vasopressor requirement, higher lactate levels, and a lower heart rate as compared to the 36°C group. A low average MAP during the first 36 hours was associated to poor outcome.

Paper V

Combining NSE with other biomarkers gave the following results: 1) In the early group, the combination of NSE at 12 hours with MR-proANP at 12 hours significantly improved the AUC:s to 0.91 (positive likelihood ratio [LR+] p-value 0.0014, net reclassification index p-value 0.003). 2) In the intermediate group, the combination of NSE at 24 hours with any biomarker did not improve the AUC of NSE (data not shown). 3) In the late group, a combination of NSE and TnT at 48 hours yielded an increased AUC of 0.98 (LR+ p-value 0.07). 4) In the mixed early and late group, a combination of NSE at 48 hours and MR-proANP at 12 hours resulted in an increased AUC to 0.97 (LR+ p-value 0.055) (table 3). PCT and prx4 did not improve the AUC of NSE at any time point (data not shown).

Table 3. Sixty-two patients with out-of-hospital-cardiac arrest of presumed cardiac cause. The best reciever operating characteristics area under curves (ROC AUC) for each single biomarker and combination of biomarkers are presented.

	AUC	**LR+ *p-value***	**NRI *p-value***
Single biomarkers:			
Early (12 h)			
CT-proAVP	0.87		
MR-proANP	0.85		
PCT	0.87		
Prx4	0.74		
Late (48 h)			
NSE	0.94		
TnT	0.60		
Combination of biomarkers:			
Early (12 h)			
NSE + MR-proANP	0.91	0.002	0.003
Late (at 48 h)			
NSE + TnT	0.98	0.07	
Mixed late (48 h) and early (12 h)			
NSE (48 h) + MR-proANP (12 h)	0.97	0.055	

LR+; positive Likelihood ratio, NRI; net reclassification improvement, MR-proANP; midregional pro-atrial natriuretic peptide, CT-proAVP; c-terminal provasopressin, , PCT; procalcitonin, Prx4; peroxiredoxin 4, NSE; neuron specific enolase, TnT; Troponin T

Summary of paper V

In this hypothesis generating study, the combination of NSE and TnT, both at 48 hours, resulted in an AUC of 0.98 for predicting outcome, although non-significant. NSE and MR-proANP, both a 12 hours yielded an AUC of 0.91 and mixing early and late sample time-points resulted in an AUC of 0.97.

Discussion

This thesis focuses on the post-cardiac arrest syndrome and its effect on; 1) the release of an array of biomarkers of stress, inflammation, heart injury, and oxidation (paper I, II and V), 2) outcome and hemodynamic profiles at two different target temperatures (paper IV), and 3) severity of shock and outcome in patients with moderate chock on admission when treated at two different target temperatures (paper III). The biomarker studies were conducted in a cohort of mild hypothermic patients (33°C). Paper III and IV are predefined post-hoc analyses of the state of the art, multicentre TTM-trial that provided a unique possibility to investigate the effect of two different target temperatures (33 and 36°C) on hemodynamics in a well defined study population [10].

Biomarkers

The first two papers investigated different biomarkers, several not tested in this context earlier, in post-resuscitation comatose cardiac arrest patients. We attempted to correlate their release profiles to the magnitude of the PCAS. Our results showed that PCT, CT-proAVP, MR-proANP, and prx4 are released very early and CT-proAVP, MR-proANP, and prx4 have their highest concentrations already at admission, while PCT reaches a plateau within 12-24 hours. CRP, on the other hand, rises in concentration more slowly and continues to rise during the first 72 hours.

We analysed the complete release profiles of investigated biomarkers during the first 72 hours sampling at eight specific time-points. This is uncommon compared to many other studies that usually only sample at one or a few time-points [115, 117, 118, 125, 126, 153]. Furthermore, few studies exist of the analysed biomarkers in the cardiac arrest setting and MR-proANP, prx4, and CRP had not been analysed in this context previously.

We showed that PCT increased to very high levels in patients with poor outcome. The release was delayed and did not soar until 6-12 hours following cardiac arrest, which is in analogy to previous research regarding induction and

production of this pro-hormone in bacterial infections [135]. PCT is marketed as a marker of infection but it is also increased in critical illness such as cardiogenic shock, cardiac surgery, and cardiac arrest without evidence of infection [136, 220, 221]. This study confirms these results since no association of PCT to three different definitions of infections was found. Instead, PCT levels seemed to be associated to surrogate markers of the PCAS, confirming our hypothesis.

There were large, significant differences in the release of PCT at all tested time points. Best discrimination was found at 12 hours following cardiac arrest with a rather impressive AUC of 0.88. Relevant cut-off levels for either poor or good outcome could not, however, be identified. We analysed patients that diverged (high PCT concentrations and good outcome) and searched for signs of infection, for example before inclusion, but were not able to identify any such confounders. The prognostic value of PCT in cardiac arrest is similar to other studies of similar size and methodology [114, 118]. One limitation of PCT as a prognostic marker is that the purpose for its induction in all parenchymal cells upon stimuli is largely unknown. Further research is needed to clarify this before PCT could be used for prognostication in cardiac arrest.

CT-proAVP (copeptin) is co-released in equimolar concentrations as vasopressin upon hemodynamic or osmotic stimuli [139]. Due to the dramatic neurohumoral response, cardiac arrest is considered to represent maximal stress in humans [33]. We found increasing concentrations of CT-proAVP in patients with poor outcome and a correlation of CT-proAVP levels to surrogate markers of the PCAS. This is not surprising since previous research has shown increased concentrations of CT-proAVP in numerous critical illnesses such as ischemic stroke [141], traumatic brain injury [142], heart failure [143], AMI [144], pneumonia [145] and shock [139]. Furthermore, elevated CT-proAVP concentrations have been found to correlate with increasing severity of sepsis [139], pneumonia [145] and pre-eclampsia [146].

CT-proAVP elevations correlated to poor outcome very early, but no relevant cut-off concentrations were identified. This is analogy to the study by Ostdal and co-workers who measured copeptin at admission and found an AUC of 0.81 [117].

Most interest in prognostication with biomarkers have focused on brain-derived biomarkers since this is the most common mode of death according to many studies [10, 88, 89, 105]. If prognosticating is carried out late, at 4-5 days after the cardiac arrest, a brain-derived biomarker could suffice since most, but not all, patients that die of other causes are already deceased [88]. If an attempt to prognosticate the outcome is done during the first 1-2 days, then all modes of death have to be included in the prognosticating algorithm since as much as 45% die from an early circulatory shock [105]. In paper V we combine different biomarkers with NSE in an attempt to, 1) add precision to prognostication at 48 hours after cardiac arrest or, 2) make an accurate prognostication of outcome earlier (at 12 or 24 hours) following cardiac arrest. This was a hypothesis

generating study for which we selected patients that fulfilled the TTM-trial inclusion criteria [10].

Although the cohort in paper V was small, we found several interesting results. First, the addition of cardiac injury specific TnT improved prognostic accuracy of NSE at 48 hours following cardiac arrest. The AUC improved from 0.91 to 0.98, although not significant. If we added the cardiac early biomarker MR-proANP, released during distension of the atria and ventricles, to NSE at 48 hours we also increased the prognostic accuracy, although not significant. Second, the combination of NSE and MR-proANP, both at 12 hours, increased their individually quite poor prognostic capabilities to a combined AUC of 0.91. This is similar to the prognostic accuracy of a single NSE concentration at 48 hours, which is the most commonly used strategy today.

We believe that the combination of biomarkers is an expanding area of interest and a requirement if we search for very high prognostic accuracy at any time point. To accept single or combinations of biomarkers as sole constituents in cardiac arrest prognostication is, however, not advisable. Prognostication must always relay on a multimodal approach including at least anamnestic information, neurological examination, and possibly biomarkers [16]. The possibility of a non-convulsive status epilepticus also has to be considered in comatose patients, which necessitates an EEG examination [222].

Outcome and hemodynamic profiles at two different target temperatures

This study (paper IV) was a predefined post-hoc analysis to the TTM-trial and we investigated a cohort of 920 patients in which we had complete vasopressor data during the intervention (0-36 hours). The patients could at worst have a moderate shock on admission since patients with a severe state of shock were excluded [10].

Patients in the 33°C group had a higher vasopressor requirement, lower heart rate, and higher lactate levels as compared to the 36°C group. Although no differences in average MAP was found for the entire intervention period, the 33°C group had a lower MAP during rewarming (lasted 8 hours). Also, we found no differences in central venous saturation between targeted temperature groups. The central venous saturation analysis was, however, complicated by a significant amount of missing data.

These results are somewhat similar to the only previously randomised, larger study on hemodynamic effects of two different target temperatures (33°C vs. no temperature control) in 77 patients [8]. They found the same reduction in heart rate

and no effect on MAP, both findings in concordance with our results. The difference being, that Bernard and co-workers targeted a MAP of 90-100 mm Hg while the TTM-trial had no such hemodynamic targets in the protocol. Also, they found no elevation in lactate but instead found a lower pH in the 33°C group. The adrenaline used to accomplish their target MAP could be a confounding factor since adrenalin can induce lactate production [223]. Furthermore, Bernard and co-workers found a reduced cardiac index in the 33°C group which could be the reason for the increased use of vasopressors in our study.

Other studies investigating the target temperature effects on the circulation most studies report positive effects of a lower temperature such as; better cardiac function [167, 169, 173, 174], improved oxygen delivery [14, 166, 169, 170, 172, 174], and reduction of vasopressor requirements [11], although conflicting results also exists [12].

One explanation for our conflicting results is that we compared two controlled target temperatures, both below or in the lower range of normal body temperature, and that the positive effects of 33°C may be evident already at 36°C [224]. The main advantage might thus be to avoid fever, as suggested by a randomized study in septic shock patients [225]. This theory is challenged by Schwarzl and co-workers who compared hemodynamics in pigs at 33°C and 38°C (normothermia) after cardiac arrest, and found improved systolic function and a favourable effect on the systemic oxygen supply-demand balance with lower temperature [170]. In another study, a variable optimal target temperature between 32.9-35.0°C could be determined for best cardiovascular performance in each individual patient [173].

The TTM-trial showed no positive effect of targeting a lower temperature on overall outcome and paper IV did not indicate any positive effects on the circulation either. On the contrary, increased vasopressor requirements and lactate levels could possibly be detrimental to patients allocated to the 33°C group.

When analysing average MAP for the entire cohort of patients, a lower MAP was, after adjustment for baseline characteristics, associated with a worse outcome. If these results can be confirmed in future studies targeting hemodynamic interventions, this could change the post-resuscitation treatment recommendations for cardiac arrest patients. Current recommendations suggest a MAP of > 65 mm Hg and find support of this target in studies on patients with sepsis [154]. In cardiac arrest, a few retrospective studies exist that support our results and report a better outcome if MAP is higher [226, 227].

The effect of 33 versus 36°C on patients with shock on admission

Contrary to our hypothesis, we found no benefit of targeting a lower temperature in 139 patients with moderate shock on admission in this predefined post-hoc analysis of the TTM-trial [10]. When published, the main trial showed no significant differences in outcome at the end-of-trial when analysing the predefined subgroup of patients with shock on admission.

The results in paper III showed a tendency of increased short-term mortality in targeting 33°C that became significant after adjusting for baseline characteristics. The data that was available regarding hemodynamic effects, such as vasopressor requirements and lactate levels were in favour of targeting 36°C. Unfortunately, no invasive hemodynamic data was collected since this was not required by the TTM-trial protocol [10]. We found no reduction in heart rate in this shock-cohort as we did when analysing the hemodynamics in all 920 patients (paper IV). The reason for this is unknown to us. It is almost universally found in human and animal studies that hypothermia worsens diastolic function [111, 165, 166, 177, 228]. A lower heart rate might reduce the negative effect of induced diastolic dysfunction. Indeed, the diastolic dysfunction was exacerbated when pacing hypothermic pigs [168, 170]. It could be that these fragile patients in moderate shock compensates their reduced stroke volume with an increased heart rate and therefore do not display any reduction in heart rate.

Our results somewhat contradict recent studies reporting the safe use of induced hypothermia in shock patients after cardiac arrest [12-15]. No explicit recommendations in guidelines exist regarding patients in shock [5, 60].

In our study, the definition of shock was a systolic blood pressure below 90 mm Hg for more than 30 minutes, or the need of supportive measures to maintain a blood pressure ≥ 90 mm Hg, and/or signs of end-organ hypoperfusion. No consensus exists as to the exact definition of shock and it is well known that systolic blood pressure is not adequate. In our cohort we chose the term ‘shock’ as opposed to cardiogenic shock since we do not know the relative influence of cardiogenic shock as compared to distributive shock. To separate these entities, invasive monitoring is needed. These discrepancies could account for some of the different results in our study as compared to others.

Limitations

There are several study limitations. In paper I, II and V: First, the relatively small cohort of patients in which part of the data was retrieved from hospital

records retrospectively. Second, there is no agreement on the definition of early onset pneumonia, which may over- or under estimate the incidence observed in our study. Also, there is an overlap between clinical signs of infection and the PCAS, which adds to the problem. To circumvent this, we used three different definitions of infections. Third, no corrections were made for age or renal function in the CT-proAVP analysis, which is in analogy with other studies of similar size in the cardiac arrest setting. [117, 131] Fourth, we lack complete data on cardiac function since not all patients had invasive cardiac output monitoring or echocardiography, which makes the MR-proANP interpretation less accurate. Fifth, the use of time to ROSC and circulation-SOFA score as surrogates for the PCAS could be questioned. Sixth, a cut-off point with 100% for poor outcome with a reasonable sensitivity could not be identified in these pilot studies. Finally, the samples were frozen before analysis with long storage times as outlined above, which could affect the accuracy of the measurements. Strengths of the present studies include prospective collection of data, serial sampling and badge analysis from a well-defined patient cohort.

In paper III and IV: First, the patients represented in paper III were not randomized according to the presence or absence of shock. Second, our results in paper III apply to patients with moderate shock since an irreversible severe shock state (systolic blood pressure < 80 mm Hg despite all supportive measures) was an exclusion criterion. Third, missing data included exact MAP on admission, exact vasopressor doses, continuous hemodynamic monitoring, protocolled echocardiography data, and time to resolution of shock. Fourth, the pragmatic trial design that allowed participating ICUs to treat patients according to their standard of care with regard to choice of sedation. One possible cause of the more pronounced cardiovascular dysfunction in the 33°C group could be that this group required more sedation, which negatively influences cardiac contractility and systemic vascular resistance, but the opposite may also be true [229]. Reduced clearance and prolonged half-life of sedatives and opiates in the 33°C group may also have contributed [230]. We have no data on the dose and doses and type of sedation used, but the sites were instructed to treat the groups similarly. Surrogate markers for use of sedative drugs, such as the number of days sedation was judged to affect evaluation of consciousness or the presence of shivering did not differ between groups [10]. The pragmatic design is also a strength of the study since it demonstrates the effect of targeted temperature management in shock patients following OHCA in routine daily practice. Finally, the relatively small sample size of patients in shock on admission in paper III allows for risk of random error and lack of power to detect real but non-statistically significant differences.

Conclusions

i. Procalcitonin concentrations increase rapidly in patients with poor outcome after resuscitation from cardiac arrest and may serve as an early predictor of poor outcome.

ii. Increasing PCT and CRP concentration during the first 72 hours after cardiac arrest are probably correlated to the PCAS and not due to early infection.

iii. CT-proAVP, MR-proANP, and Prx4 concentrations all increase rapidly and are significantly higher in patients with poor outcome.

iv. CT-proAVP may serve as an early predictor of poor outcome.

v. The addition of biomarkers to NSE may improve prognostication accuracy, although further studies are warranted.

vi. Patients allocated to targeted temperature management at 33°C had higher vasopressor requirements, higher lactate levels, and lower heart rates as compared to the 36°C group.

vii. Low average MAP during the first 36 hours was associated to poor outcome.

viii. Patients with shock on admission had no benefit of targeted temperature management at 33°C as compared to 36°C. After adjustments for baseline characteristics, a significant increase in ICU mortality was observed in the 33°C group, although there were no significant differences in long-term outcome.

ix. Lactate levels and requirement for vasopressors, which we consider surrogate markers of severity of shock, were higher in the 33°C group in patients with moderate shock on admission.

Future aspects

Biomarkers

Currently, no single reliable biomarker exists to predict either poor or good outcome at any time following cardiac arrest. We believe that no single biomarker can encompass all modes of death following cardiac arrest and that we need to consider different combinations of biomarkers to aid in prognostication. We plan to implement a similar methodology as in paper V in the TTM-trial cohort and investigate if any combinations of biomarkers could be useful as prognostication tools. Predicting a poor outcome is important, but it is also of value to be able to predict a good outcome. For instance, if a brain-derived biomarker could be identified that could predict good cerebral outcome with certainty at admission, this could motivate emergency invasive strategies to treat myocardial dysfunction and an early strategy to prolong care.

If a novel biomarker or combinations of biomarkers are identified, its potential should be evaluated in prospective studies with a preset cut-off concentration. This cut-off level must not necessarily have a false positive rate of zero for poor outcome since we expect that there will always be outliers. Up to a 5% false positive rate could probably be accepted and still be of clinical use since biomarkers always should be used in combinations with other prognostic tools. Prognostication should be based on a multimodal approach including a clinical neurological examination at least on or two other tools, preferably neurophysiology and biomarkers according to the Lund protocol.

Hemodynamics

Very little research in post-resuscitation cardiac arrest patients has investigated optimal cardiovascular treatment and if any specific hemodynamic targets could improve outcome. We hope that further research will focus on specific interventions such as pre-specified hemodynamic goals and prospectively evaluate their effect on outcome. Also, prospective randomised studies are needed to study the effect of different target temperatures on cardiovascular performance employing invasive cardiac output monitoring.

A selected subset of patients could also, be eligible for minimally invasive left ventricular assistance devices and extracorporeal life support, but larger, randomised studies are lacking. Since most of the cardiac dysfunction is believed to be a result from stunning and this is normally reversible in the first 48-72 hours, recovery of cardiac function is anticipated [110, 111]. Further investigations in this area could be rewarding since the mortality in these patients is very high.

Summary in Swedish

Populärvetenskaplig sammanfattning

Hjärt-kärlsjukdom är den vanligaste dödsorsaken i världen och orsakar enligt Världshälsoorganisationen 7,4 millioner människors död varje år. I Sverige påbörjades Hjärt-lungräddning (HLR) hos mer än 5000 personer som drabbats av hjärtstopp utanför sjukhus under 2013. Av dessa överlevde cirka 500 personer eller cirka 10 %. Överlevnaden efter hjärtstopp har förbättrats varje år det senaste decenniet vilket troligen beror på ökad medvetenhet hos allmänheten och att fler påbörjar HLR. Även Räddningstjänsten rycker numera ut vid medicinsk sjukdom i de fall ambulansen bedöms ha lång framkörningstid (Region Skåne).

Under tiden hjärtat står stilla finns ingen eller mycket liten cirkulation till hjärnan och övriga kroppen och leveransen av syre till cellerna upphör. Man förlorar medvetandet redan efter några sekunder och efter några minuter börjar skador uppstå som blir oåterkalleliga. Hjärnan är extra känslig eftersom den är nästan helt beroende av syre för sin energiomsättning medan resten av kroppen klarar sig kortare stunder utan syre och kan växla över till så kallad anaerob energiomsättning. HLR ger en viss cirkulation med syresatt blod vilket kan förlänga den tid som hjärnan, hjärtat och den övriga kroppen klarar sig utan skador. Det är dock avgörande att hjärtaktiviteten återkommer inom en inte allt för lång tidsrymd. I väntan på att det ska ske måste HLR utföras med god kvalitet, vilket innefattar kraftfulla bröstkompressioner av tillräcklig frekvens (≈100/min).

Endast en av tio som återfår egen cirkulation vaknar upp direkt efter hjärtstoppet medan majoriteten av patienter är fortsatt medvetslösa vid ankomst till sjukhus. Av alla som återfår cirkulationen efter framgångsrik HLR överlever mellan 40-50%. Dödsorsaken är i de flesta fall hjärnskada och dessa patienter återfår aldrig medvetandet. En mindre andel dör av svår hjärtsvikt och/eller cirkulatorisk chock och då inträffar vanligtvis döden inom de första dagarna.

De patienter som inte återfår medvetandet direkt vårdas på en intensivvårdsavdelning i respirator. Man vet att feber är skadligt och försämrar hjärnans förmåga att återhämta sig. För att minska hjärnskadan och förbättra överlevnaden så har hjärtstoppspatienter sedan 2002 kylts ned till 33°C under 12-24 timmar. En viss osäkerhet har dock funnits och en nyligen publicerad studie visade att behandling vid 36°C var lika bra som behandling vid 33°C. Då vi i likhet med många andra sjukhus anser att 36°C innebär mindre risker behandlas

numer patienterna i Skåne vid denna temperatur. Andra sjukhus har gjort en annan bedömning av forskningsresultaten och fortsätter tills vidare att behandla vid 33°C.

Det är svårt att förutsäga utgången och vilka möjligheter som finns till återhämtning i det tidiga skedet efter hjärtstopp då patienten är medvetslös. För att kunna ta ställning till fortsatt vård och ge bästa möjliga information till anhöriga krävs därför att man gör upprepade bedömningar och en prognostisering. Tidpunkten för denna prognosbedömning har debatterats men många anser att man inte bör göra den tidigare än 3 dygn efter det att temperaturbehandlingen avslutats, det vill säga 4-5 dygn efter hjärtstoppet. Om man väljer att göra prognosbedömningen tidigare är det ännu viktigare att ta hänsyn till effekten av sömnmedel och smärtstillande medicinering som getts under kylbehandlingen eftersom dessa kan finnas kvar och påverka utfallet av undersökningarna. Vid prognosbedömning ingår en klinisk neurologisk undersökning omfattande nervfunktion i ögon och ansikte samt reaktion på smärtstimulering, olika neurofysiologiska mätmetoder och ofta analys av blodprov (så kallad biomarkör).

En biomarkör är en substans, oftast äggviteämne, som kan mätas i olika kroppsvätskor, ofta blod. Optimalt ska en biomarkör frisättas omedelbart vid skada och vara enkel att mäta, billig och pålitlig. Vid prognosbedömning efter hjärtstopp har framför allt olika markörer studerats som frisätts vid hjärnskada. Neuron specifikt enolase (NSE) är den biomarkör som oftast används men tyvärr har den också vissa brister, vilket inneburit att intresset för forskning avseende andra biomarkörer har varit stort.

Vi har valt att studera biomarkörer som frisätts vid stress (CT-proAVP), inflammation (procalcitonin), oxidation (peroxiredoxin) och hjärtpåverkan (MR-proANP) efter återupplivning. Vi fann att alla dessa biomarkörer i blod var mycket högre hos de patienter som dog och att frisättningen var associerad till graden av organpåverkan. Vi undersökte också om det kunde finnas en vinst med att kombinera olika biomarkörer för att på så sätt kunna förbättra prognosbedömningen. Våra preliminära resultat visade att så var fallet.

Vi har i två studier undersökt vilken effekt de båda testade behandlingstemperaturerna 33 och 36°C har på blodtryck och på cirkulationen. Vi fann att patienterna som behandlades vid 33°C hade ett större behov av blodtryckshöjande medicinering samt tecken på försämrad cirkulation. Vi såg också att ett lågt blodtryck de första två dygnen korrelerade med sämre prognos.

Vi undersökte sedan de patienter som hade cirkulatorisk chock vid ankomst till intensivvårdsavdelningen. Patienter i 33°C gruppen hade tendens till ökad tidig död, men det fanns inga säkra skillnader avseende överlevnad på längre sikt. Under de första sju dygnen på intensivvårdsavdelningen hade 33°C-gruppen ökat behov av blodtryckshöjande medicinering och hade tecken till försämrad cirkulation. Sammanfattningsvis så fann vi att temperaturbehandling vid 36°C tycks vara mer fördelaktigt än 33°C i vår studie.

Vi planerar att i en nära framtid gå vidare med att undersöka hur olika biomarkörer på bästa sätt kan kombineras för att förutsäga utgången hos enskilda patienter och om detta kan ske vid en tidigare tidpunkt än idag. Vidare så hoppas vi på ett ökat intresse för forskning kring hjärtstopp och nya studier avseende optimal behandling av patienter i cirkulatorisk chock efter återupplivning.

Acknowledgments and Grants

It is a pleasure to thank the many people who made this thesis possible.

It is difficult to overstate my gratitude to my friend, tutor and scientific mentor, **Hans Friberg**, whose expertise, understanding, and patience, added considerably to my dissertation experience. I appreciate your inspiration, insightfulness, and determination in research, and great assistance in writing my papers.

My co-tutors; **Niklas Nielsen** for letting me be you for a while – it was a great experience! **David Erlinge** for your cardiovascular expertise and invaluable input. Thanks!

Johan Persson, ICU director and friend, for supporting this research project and, even more, my ICU career. You have shown me in challenging situations what our profession is all about and what really matters.

My predecessor in biomarker research, **Malin Rundgren** whose impressive cardiac arrest thesis paved the way for my projects. Thanks for sharing your knowledge in both science and intensive care medicine.

Susann Ullén, **Fredrik Nilsson** and **Gustav Smith** for your invaluable support in interpreting my data and statistical analysis. Thanks for guiding me through the dark abyss of statistics. I´ve learned much!

Co-authors **Josef Dankiewicz** and **Tobias Cronberg** for key discussions and important contributions to the presented papers.

Institution professor **Mikael Bodelsson** for getting me interested in anaesthesiology and intensive care to begin with. Thanks for giving me the opportunity to work as assistant professor during the last year and for all support throughout this process. Senior professors; **Per-Olof Grände** for showing me what a professor in Lund can accomplish by applying sound physiologic principles to treat disease and **Dag Lundberg** for your wisdom and guidance.

Past and present heads of the Department of Anaesthesia and Intensive Care; **Görel Nergelius**, **Bengt Roth**, and **Marie Martinsson** for the opportunity to complete this thesis and clinical support, and **Carolina Samuelsson**, for continuing to make research an integral part of the department.

My friend and former clinical supervisor **Per Flisberg** for looking after me when I was new at the department and showing me all the tricks at work, in life and on the golf course.

My roommate, dear colleague and co-assistant professor **Dag Winstedt** – for great discussions about life, research and everything in-between. It has been a true pleasure.

The eminent **Björn Bark** for showing me that nothing is impossible and that research can be easy. To **Sofus Rabow** for reminding me of my heritage and giving me precious research time. For camaraderie!

To all my **colleagues** for making everyday at work a true pleasure.

To **Anne Adolfsson** for your support and expertise in conducting clinical trials and the **ICU staff** for making this research project possible and always doing your best no matter what.

To **Laila** and **Lennart**, **Ida** and **Martin**, **Johan** and **Emma**, and not least **Olle** – for all the cheers.

My parents, **Gunilla** and **Mats,** and my sister **Karin** – for unconditional love and for encouraging my studies from the very beginning.

My beloved wife **Anna**, for never-ending support and understanding. This would not have been possible without you!

My big sons, **Nils** and **Erik**, and my little princess **Vera;** the treasures of my life, for constantly making me happy and giving my life a purpose. Couldn´t love you more!

In conclusion, I recognize that this research would not have been possible without the financial assistance from Skåne county council´s Research and Development Foundation and the European Union funding through Interreg IV a.

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