Therapeutic Hypothermia After Out-of-Hospital Cardiac Arrest

- implementation and clinical management-

Michael Busch

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Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest

Faculty of Medicine

Institute of Surgical Science

University of Bergen, Norway

Stavanger University Hospital
Stavanger Hospital Trust

Department of Anesthesiology and Intensive Care

Stavanger University Hospital

Stavanger, Norway

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Real knowledge is to know the extent of one´s ignorance

Confucius

Abbreviations

OHCA – Out-of-Hospital-Cardiac Arrest

IHCA – In- Hospital-Cardiac Arrest

ILCOR – International Liaison Committee on Resuscitation

ERC – European Resuscitation Council

TH – Therapeutic Hypothermia

ICU – Intensive Care Unit

NIR – Norwegian Intensive Care Registry

STEMI – ST-elevation myocardial infarction

PCI – Percutaneous coronary intervention

CPR – cardiopulmonary Resuscitation

BLS – Basic Life Support

ACLS – Advanced Cardiac Life Support

ROSC – return of Spontaneous Circulation

PEA – Pulseless Electric Activity

HACA – Hypothermia After Cardiac Arrest Study Group

GCS – Glasgow Coma Score

CPC – Cerebral Performance Category

Abstract

Background: With the publication of two randomized controlled trials (RCTs) in 2002, therapeutic hypothermia (TH) was re-introduced in postresuscitation care of comatose out-of-hospital cardiac arrest (OHCA) patients. Many issues, however, were unresolved, including implementation protocol, cooling technique, clinical management, implications of TH treatment on prognostic accuracy and therapeutic benefit in subgroups of OHCA excluded from the initial RCTs. **Objectives:** We wanted to study the implementation of therapeutic hypothermia into daily practice, provide information on clinical management, including differences in cooling techniques and test application in elderly OHCA patients excluded in earlier trials. **Subjects:** We evaluated the clinical management of adult comatose OHCA patients who were treated in our ICU (paper I and IV). In paper II we surveyed our intensive care nursing staff with regard to key nursing aspects of different cooling methods and devices. In paper III, ICU consultants were assessed on their prognostic approach in OHCA patients treated with TH. **Methods:** In paper I we retrospectively compared OHCA patients treated with TH with a historic control group of OHCA patients fulfilling the TH inclusion criteria. We collected Utstein template data, as well as data on ICU-and hospital length of stay (LOS), incidence of adverse events, and outcome at hospital discharge and after one year. In paper II an anonymous survey was conducted with our intensive care nursing (ICN) staff, assessing ease of application, hygiene, work load, noise level and visual patient monitoring of four different cooling methods. In paper III we used a semi-structured telephone interview to conduct a nation-wide survey of the prognostication approach of comatose OHCA patients involving timing, methods, involved specialties and rating of prognostic methods. In paper IV we retrospectively studied outcome variables in all adult OHCA patients treated with TH in our ICU over a six-year period, who fulfilled the Hypothermia After Cardiac Arrest study (HACA) criteria with exception of the upper age limit. **Results:** With our simple cooling protocol we achieved 100% implementation and successful attainment of target temperature (TT) in 89% of patients (paper I).

However, it took median 7, 5 hours (1-10 h) to reach TT, which was maintained for median 10 hours (6-19h). Demographics, Utstein template data, ICU and hospital LOS did not differ significantly between the two groups. Insulin resistance and hypokalemia were significantly more frequent in the TH group, whereas seizures were observed more frequent in the normothermia group. The TH group showed significantly higher rates of survival to hospital discharge (59% vs. 32%, p = 0, 05). In paper IV we found that although older age influenced outcome, over half of OHCA patients older than 75 years showed favorable outcome at hospital discharge. The four cooling methods used in our department differed significantly regarding key nursing aspects (paper II). Our simple cooling method scored high regarding ease of application and noise level, but low in work load and hygiene. The CoolGard and ArticSun systems scored highest in work load and hygiene. Only 53% of ICNs were satisfied with their initial training and merely 10% felt adequately prepared at the time when TH was introduced. In paper III we found that even after introduction of TH, prognostication after OHCA was performed within 48 hours in the majority of patients. More than one specialty was involved, using mainly clinical neurological examination (100%), prehospital data (76%), cerebral computer tomography (CCT) (58%) and electroencephalography (EEG) (52%) findings. Somatosensory evoked potentials (SSEP) (8%), biochemical markers (8%) and magnetic resonance imaging (MRI) (8%) only played a minor role. Only one ICU used a standardized protocol. **Conclusions:** Our simple external cooling protocol could be rapidly implemented, was safe, cheap and feasible, but not optimal with regard to accurate temperature management (paper I). Key nursing elements differed significantly among available cooling methods (paper II). Even though age influences outcome, more than half of our OHCA population older than 75 years showed good outcome. The limitation of patient eligibility for TH treatment should not be based on age alone (paper IV). Despite frequent use of TH, prognostication after OHCA was executed early, mainly based on clinical examination, prehospital data, CCT and EEG results. SSEP seems to be underused and underrated, whereas the clinical accuracy of CCT, prehospital data and EEG seems to be overrated (paper III).

List of publications

1. Busch M, Søreide E, Lossius HM, Lexow K, Dickstein K. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. Acta Anaesthesiol Scand 2006; 50:1277-83

2. Våga A, Busch M, Karlsen TE, Nilsen OB, Søreide E. A pilot study of key nursing aspects with different cooling methods and devices in the ICU. Resuscitation 2008;76: 25-30

3. Busch M, Søreide E. Prognostication after out-of-hospital cardiac arrest, a clinical survey. Scand J Trauma Resusc Emerg Med. 2008; Sep 15;16(1):9

4. Busch M, Søreide E. Should advanced age be a limiting factor in providing therapeutic hypothermia to cardiac arrest survivors. A single-center observational study. Therapeutic Hypothermia and Temperature Management 2011; 1: 29-32

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Contents

1. Introduction

1.1 Sudden cardiac arrest

For the greater part of human history, mankind believed that death is irreversible. Even though anatomical and pathophysiological essentials of cardiac arrest were known for centuries, it took until the 1960s before cardiopulmonary resuscitation (CPR) with artificial ventilation, mechanical chest compressions and defibrillation became a clinically practicable concept.[1]

Sudden cardiac arrest implies a death from natural causes, characterised by three elements: natural process, rapid progress and unanticipated occurrence ensuing less than one hour from the onset of symptoms.[2] The International Liaison Committee on Resuscitation (ILCOR) defines cardiac arrest as the „cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation".[3]

Circa 275.000 Europeans experience sudden cardiac arrest treated by the emergency medical services (EMS) per year.[4] With the cessation of circulation, starts a process, which, if no intervention is performed, ultimately leads to death. Usually, there are two recognised systems of "biological death": a) irreversible cardiac arrest and b) brain death.[5] Thus, within the time frame between cardiac arrest and the development of irreversible neurological injury, resuscitative efforts have to be commenced if meaningful survival is pursued.

In cases of sudden cardiac arrest, the patient has usually functional vital organs systems and most commonly unrecognized ischemic heart disease.[6,7] Other causes of sudden cardiac arrest include arrhythmic heart disease, cardiomyopathy, inflammatory myocardial disease, valvular disease, pulmonary diseases, pulmonary embolism,

cerebral nervous system disease, vascular catastrophies, drugs, toxins, trauma, non-traumatic bleeding and drowning.[8,9]

1.1.1 Types of cardiac arrest

Several types of cardiac arrest can be differentiated: adult vs. paediatric, presumed cardiac origin vs. non-cardiac origin, in-hospital (IHCA) vs. out-of-hospital (OHCA). The various types of cardiac arrest differ significantly in incidence, aetiology, prognosis and causes of mortality.

Paediatric cardiopulmonary resuscitation differs from adult CPR, as children present different anatomy, physiology and pathogenesis of cardiac arrest. Most paediatric cardiac arrests are secondary to hypoxia or circulatory failure; nevertheless 7-10% are precipitated by ventricular fibrillation or tachycardia.[10] Recent data suggests a 10% chance of survival to discharge in patients over 1 year and OHCA.[11] The majority of adult patients experiencing cardiac arrest suffer from cardiac disease, mainly unrecognised ischemic heart disease.[7] Non-cardiac arrest aetiology is reported in 25%-34% and it includes trauma, non-traumatic bleeding, intoxication, drowning, obstructive pulmonary disease and pulmonary embolism.[8,9,12] The survival rate of non-cardiac arrest is substantially lower than survival after cardiac arrest of cardiac origin. [8] Cardiac arrests are usually classified as in-hospital (IHCA) or out-of-hospital (OHCA) according the location of the cardiac arrest. In-hospital and out-of-hospital cardiac arrest differ significantly in incidence, aetiology, prognosis and causes of mortality.[13]

In addition, the first recorded electrocardiographic (ECG)-rhythm is often used to categorize cardiac arrest. There are four main rhythms associated with circulatory arrest: ventricular fibrillation (VF), non-perfusing ventricular tachycardia (VT), pulseless electrical activity (PEA) and asystole. The first two are usually grouped together as “shockable rhythm”.[14] VF is described as uncoordinated heart action with a high metabolic demand and lack of effectual contractions.[15] Pulseless electric activity (PEA) is characterised by absent central or peripheral pulses and an

electrocardiographic rhythm other than VF/VT. Asystole is defined by the absence of pulses and electrocardiographic activity. The different cardiac rhythms are strong indicators of survival and outcome. Patients found in VF or non-perfusing VT have a significantly better chance of good outcome than patients in asystole or PEA.[16]

The incidence of VF/VT as the initial recorded ECG- rhythm is approximately 40 %.[12,16,17] The probability of the initial rhythm being VF/VT changes with the time period between onset of cardiac arrest and initial ECG, since VF fades in amplitude and regresses into asystole or PEA.[18] The overall incidence of sudden cardiac arrest and particularly the occurence of VF/VT have decreased over the past decades.[17,19]

This thesis has exclusively studied OHCA of presumed cardiac cause in adults.

1.1.2 Epidemiology of cardiac arrest

The estimated overall incidence of out-of-hospital cardiac arrest (OHCA) lies between 40 and 130 per 100.000 inhabitants per year and increases with age from 0,9 person-years for the population aged between 18-50 to 8,5 person-years for subjects aged over 80 years.[20] The incidence of EMS-treated cardiac arrests in Europe and North America is about 55/100.000 person/years for all rhythm cardiac arrest and 15/100.000 for VF cardiac arrest.[4,21]

When cardiopulmonary resuscitation is attempted, a return of spontaneous circulation (ROSC) may be achieved in 17-49% of the victims.[22] Unfortunately, ROSC is merely the first step in survival after out-of-hospital cardiac arrest. Almost 80% of patients, who initially survive, remain in a coma for varying lengths of time and are admitted to an intensive care unit (ICU).[23] Data on OHCA patients admitted to the hospital suggest a wide regional and institutional disparity in in-hospital mortality ranging from 41-90%.[24] The majority of all deaths after OHCA are due to neurological injury and myocardial dysfunction.[25,26] Even though critical care is progressing continuously, overall survival from OHCA has been stable for the last three decades.[27]

1.1.3 History and physiology of cardiopulmonary resuscitation

Throughout most of the recorded history of mankind, cardiac arrest was usually a fatal event and the natural ending of life. It was not until the end of the 18th century before resuscitation was deemed possible. However, it took more than 200 years before skills, knowledge and technology for cardiopulmonary resuscitation became a clinical reality in the 1960s.[1] Studies on artificial ventilation were already performed by Vesalius in the 16th century, but it was the work of Elam, Safar, and Gordon and the demonstration of the superiority of mouth-to-mouth ventilation over the traditionally used manual method in 1958 that convinced the medical community.[28] In 1960, Kouwenhoven and colleagues published their work on closed chest cardiac massage as a new treatment for cardiac arrest. [29] Artificial respiration and chest compression were then combined to create cardiopulmonary resuscitation (CPR) and in 1966 the Cardiopulmonary Resuscitation Committee on CPR reported its recommendations.[1] Electrical defibrillation was first successfully applied internally in 1947 and externally in 1956.[30,31] With the development of portable DC-defibrillators by Lown and colleagues, prehospital CPR was possible. [32] By the late 1960s, CRP, defibrillation and evolving emergency medicine services systems were all in place. Dispatcher-assisted CPR to direct bystanders was introduced in the late 1980s.[33] The International Liaison Committee on Resuscitation (ILCOR) was established in 1992 and provides evidence-based guidelines for basic (BLS) and advanced life support (ACLS)[34]. BLS involves chest compressions and artificial ventilation, ACLS, in addition, drug administration, defibrillation and airway management.[35]

Pathophysiology

Following cardiac arrest some blood flow continues for several minutes until the pressure gradient between aorta and right heart equilibrates. The decrease in arterial pressure and the increase in right atrial pressure lead to right ventricular dilatation and distortion of the interventricular septum. Chest compressions result in an antegrade flow in the aorta and the pulmonary artery during the compression phase and in a retrograde flow during the decompression phase. Coronary flow is reverse compared

to the flow pattern of the major blood vessels during compression and decompression. [36] Cardiac output during optimal CPR is between 25-50% of pre-arrest values. [37] CPR decompresses the right ventricle, fills the left heart and coronary arteries and mitigates end-organ ischemic injury by providing crucial organ perfusion.[38,39] Weisfeldt and Becker´s "three phase time sensitive model" of cardiac arrest focuses on optimizing treatment for cardiac arrest according to specific phases: The electrical phase where the heart corresponds to defibrillation, followed by the circulatory phase where chest compressions are required prior to defibrillation and the metabolic phase where therapies address the ischemia and reperfusion injury. [40]

The risk of poor outcome is increased by expanding time intervals between distress call and arrival of the ambulance, collapse and commencement of CPR, absence of bystander CPR as well as every minute that defibrillation is deferred. [41-43] The chain of survival for a patient in cardiac arrest contains therefore early recognition and call for help, early CPR, early defibrillation and good post resuscitation care. [14]

Figure 1. Chain of survival

Historically, most focus and resources were directed to the first three links of the chain of survival. The importance of good and early post resuscitation care has lately been recognized and several studies have associated variations in OHCA outcome to differences in post resuscitation treatment.[44-46] The 2010 resuscitation guidelines

acknowledge the major potential influence of post resuscitation care on lowering in-hospital mortality caused by post cardiac arrest syndrome.[14,47]

1.1.4 Pathophysiology of cardiac arrest and post-cardiac arrest syndrome

As blood flow ceases, cell injury is commenced by whole-body ischemia and then augmented by return of circulation, also named reperfusion. [48] The ischemic injury starts relatively slowly, then gathers momentum and finally plateaus. [49] Many of the damaging mechanisms after ischemia and reperfusion are executed over an interval of hours to several days and cellular models suggest that up to 70% of cell deaths can be attributed to reperfusion injury rather than ischemia alone. [40,50,51]

The mechanisms of global ischemia and reperfusion are diverse, complex and not fully understood, involving abrupt cellular energy exhaustion with adenosine-triphosphate (ATP) breakdown, change to anaerobic metabolism, intra-and extracellular acidosis, intracellular calcium overload, mitochondrial dysfunction, activation of intracellular enzymes, glutamate release, neuroexcitatory cascades, increased free radical production, apoptosis and inflammatory response. [52]

The distinct pathophysiological changes after cardiac arrest - termed "postresuscitation disease" by Negovsky in the late 1980`s – are characterized by four mechanisms: (1) perfusion failure, (2) reoxygenation injury, (3) extracerebral causes, like post anoxic viscera and blood stasis.[53,54] Post-cardiac arrest inflammation increases secondary neuronal damage via activation of blood coagulation and platelets as well as excessive liberation of pro-inflammatory mediators, expression of endothelial adhesion molecules, accumulation of inflammatory cells in the injured brain tissue and increased nitric oxide production.[52] The immuno-inflammatory profile of post-cardiac arrest patients resembles that of patients in sepsis.[55]

The clinical entity of pathophysiological changes has been termed *post cardiac arrest syndrome* and is causative to 87% of all in-hospital deaths after OHCA.[26] The

International Liaison Committee on Resuscitation (ILCOR) defines the four key elements of post-cardiac arrest syndrome as: (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, (3) systemic ischemia/reperfusion response, and (4) persistent precipitating pathology.[24]

Clinical symptoms of post-cardiac arrest brain injury comprise coma, seizures, myoclonus and varying degrees of neurophysiological impairment, varying from slight memory dysfunction to brain death.[24] Almost 80% of patients who initially survive an OHCA remain comatose and are admitted to an ICU, where approximately 17%-68% of patients after OHCA and 23% of IHCA will succumb to post-cardiac arrest brain injury. [23,25,26] Good cerebral outcome occurs in only 11-48% of patients discharged from the hospital. [54]

Two categories of neuronal cell death are recognised in ischemia: neuronal necrosis ensues hypoxia during the cardiac arrest, whereas apoptosis and multifocal micro infarcts characterise reperfusion injury.[56] Protracted neuronal necrosis and apoptosis – triggered by various pathways - is enhanced in selectively vulnerable neuron populations, like the hippocampus, cortex, cerebellum, corpus striatum, basal ganglia, thalamus and spinal cord. [57]

Dysregulation of cerebral blood flow (CBF) after ROSC is characterized by early hyperemia followed by a phase of delayed reduction in CBF as well as microcirculatory reperfusion failure.[58,59] The length of the hyperemic phase as well as the extent of the areas with no or reduced reflow is proportional to the duration of ischemia.[60,61] Microcirculatory reperfusion failure- also termed no-reflow- in spite of adequate cerebral perfusion pressure has been ascribed to intravascular thrombosis.[62]

Additionally, there is evidence of impaired cerebral autoregulation and disruption of the blood-brain-barrier (BBB) with edema formation.[59,63] During the subacute phase after resuscitation, cerebral vascular resistance is increased while CBF, cerebral metabolic rate of oxygen (CMRO2) and glucose consumption are decreased.[64,65]

Hypotension, hypoxia, hyperoxia, seizures, hyper-and hypoglycemia as well as hyperthermia all aggravate secondary brain damage after cardiac arrest.[24] Hyperoxic reperfusion after ROSC seems to increase oxidative stress, promote inflammation and is associated with worse neurologic outcome and increased mortality.[66-68] Hyperthermia in particular has been shown to impact outcome after cardiac arrest. For every degree of a peak temperature greater than 37°C, the risk of unfavorable outcome increases significantly.[46,69]

Post-cardiac arrest myocardial dysfunction (PCAMD) is a critical factor impacting both mortality after OHCA and neurological outcome. [26] Approximately 50% of all OHCA survivors experience PCAMD, involving systolic and diastolic dysfunction of both the right and left ventricle.[70-72] The incidence of PCAMD is related to the duration of CPR, amount of administered adrenaline, number of shocks applied, age, arrest-to-defibrillation interval, arrest-to-PCI interval and prearrest myocardial function.[26,72] Myocardial dysfunction is the primary cause of death within the 24 hours after ROSC.[26]

After re-establishment of coronary blood flow to the ischemic myocardium, reperfusion injury can occur, promoting further myocardial damage and decreasing the benefit of coronary reperfusion therapy.[26] PCAMD is caused by reversible myocardial stunning, no-reflow phenomenon, microvascular dysfunction, reperfusion arrhythmia and a profound systemic inflammatory response syndrome, usually resolving within 72 hours in OHCA survivors.[26,40,55,70] Attainment of core body temperature below 35°C before percutaneous coronary intervention (PCI) and reperfusion in cardiac arrest patients with acute coronary syndrome (ACS) was associated with a substantial reduction in infarct seize.[73]

Both early arterial hypotension, defined by a systolic blood pressure below 90 mm Hg, and absence of early goal-directed hemodynamic optimization were associated with worse outcome.[74,75]

The severe shock and global ischemia of cardiac arrest prompts activation of coagulation, platelets and endothelium as well as a systemic inflammatory response. This leads to microcirculatory dysfunction, reperfusion disorders, impaired vasotonus, adrenal dysfunction, reduced oxygen delivery, increased gut mucosal translocation, immunosuppression and ultimately multiple organ failure and death. [24,54,55] Adrie and colleagues examined the immunological status of OHCA patients and found a resemblance to patients in sepsis with high concentrations of cytokines, detection of plasma endotoxin and cytokine dysregulation.[55] Post-ischemic cerebral inflammatory response involves microglia activation, endothelial adhesion molecules production and leukocyte migration and activation.[76]

An additional factor contributing to in-hospital mortality of OHCA survivors is the persisting precipitating pathology that caused the cardiac arrest. Numerous etiologies are associated with cardiac arrest and their causal treatment is essential for the patients‘survival. Cardiac causes of arrest are presumed in approximately 80% of all OHCA, the majority suffering from unrecognised ischemic heart disease and acute coronary syndrome.[6,7] Autopsy findings suggest an acute coronary event in 57%-73% of sudden OHCA patients without chronic heart failure and in 33% of OHCA patients with chronic heart failure.[7,77,78] In contrast, merely 11% of adult in-hospital cardiac arrests were ascribed to acute coronary syndromes.[79] Non-cardiac arrest aetiology is reported in 25-34 %.[8,12] Given the high occurrence of ACS in OHCA patients, the International Liaison Committee on Resuscitation (ILCOR) recommends immediate coronary angiography (CAG) and percutaneous coronary intervention (PCI) in OHCA patients with ST-elevations myocardial infarction (STEMI) and the consideration of CAG and PCI in all OHCA patients.[24]

1.1.5 Documentation of cardiac arrest

The 1991 Utstein-style template and its 2004 update by ILCOR have been the standard for uniform reporting of OHCA for the past two decades.[3,80] Outcome data points are the percentage of patients discharged alive from hospital and the neurological status defined by the Glasgow-Pittsburgh Cerebral Performance Category (CPC).[80]

1.2 Post-cardiac arrest intensive care

Whereas the importance of the electrical and circulatory phases of Weisfeldt`s cardiac arrest model was early recognized, has the metabolic phase long been confined to establishing extracranial homeostasis by providing general supportive ICU care. [40] The 2000 ERC post resuscitation care guidelines targeted the transport of the patient to an ICU, the optimization of tissue oxygenation with cardiorespiratory support, anti-arrhythmic therapy, the identification of the cause of the arrest and the consideration of fibrinolysis or PCI in STEMI. Hypocapnia and even mild hypotension should be avoided. Electrolyte abnormalities and fever should be treated, seizures controlled. Patients who were hemodynamically stable and mildly hypothermic (> 33°Celcius) should not be actively warmed but hypothermia should not be induced after cardiac arrest.[81] The importance of good and early post resuscitation care has lately been recognized and several studies have associated variations in OHCA outcome to differences in post resuscitation treatment.[44-46]

In the attempt to mitigate the reperfusion injury, a wide array of neuroprotective medications has been studied without leading to evidence that they improve outcome after OHCA.[24]

The simultaneous publication of two landmark studies in 2002 showed that reduction of core temperature to 32°C-34°C for 12-24 hours, obtained within hours after return of spontaneous circulation (ROSC) in VF-OHCA, improved survival and neurological

outcome.[82,83] The International Liaison Committee on Resuscitation (ILCOR) acknowledged the published evidence by making an advisory statement in 2003 recommending cooling adult unconscious VF-OHCA survivors to 32°C-34°C for 12-24 hours. Additionally, it was stated that hypothermia could be beneficial in cardiac arrests presenting with other rhythms than VF and in in-hospital cardiac arrest.[84] The re-discovery of hypothermia treatment in post resuscitation care sparked a paradigm shift from cardiopulmonary resuscitation (CPR) to cardiopulmonary-cerebral resuscitation (CPCR) and a new interest for neuroprotective measures in intensive care medicine. [85]

1.3 Therapeutic Hypothermia

Therapeutic hypothermia (TH) is defined as "the controlled lowering of core temperature for therapeutic reasons".[86] Temperature ranges for hypothermia are categorized as: mild (34°C-35,9°C), moderate (32°C -33,9°C), moderate-deep (30°C-31,9°C) and deep (< 30°C).[87]

Several others synonyms for therapeutic hypothermia used in the literature are controlled hypothermia [88], induced hypothermia [86], mild hypothermia [89], and targeted temperature management. [90]

TH was introduced in the operating room in the 1950s as a neuroprotective measure for intracerebral aneurysm procedures and for cardiac surgery involving complete cardiac arrest.[91-94] Studies on the use of resuscitative hypothermia after cardiac arrest outside the operating room in a small number of patients were conducted in the late 1950s. In 1964, Peter Safar recommended to start TH within 30 minutes in comatose cardiac arrest survivors in his "first ABCs of resuscitation" (fig.2).[95-97] In their review on the treatment of the comatose patient, Rosomoff and Safar provide early guidelines for neurointensive care stating that fever is harmful, temperature rises above 38°C should be avoided by external cooling and "hypothermia seems indicated in any

patient who has brain damage severe enough to produce unconsciousness- usually the temperature is kept at 32°C".[96]

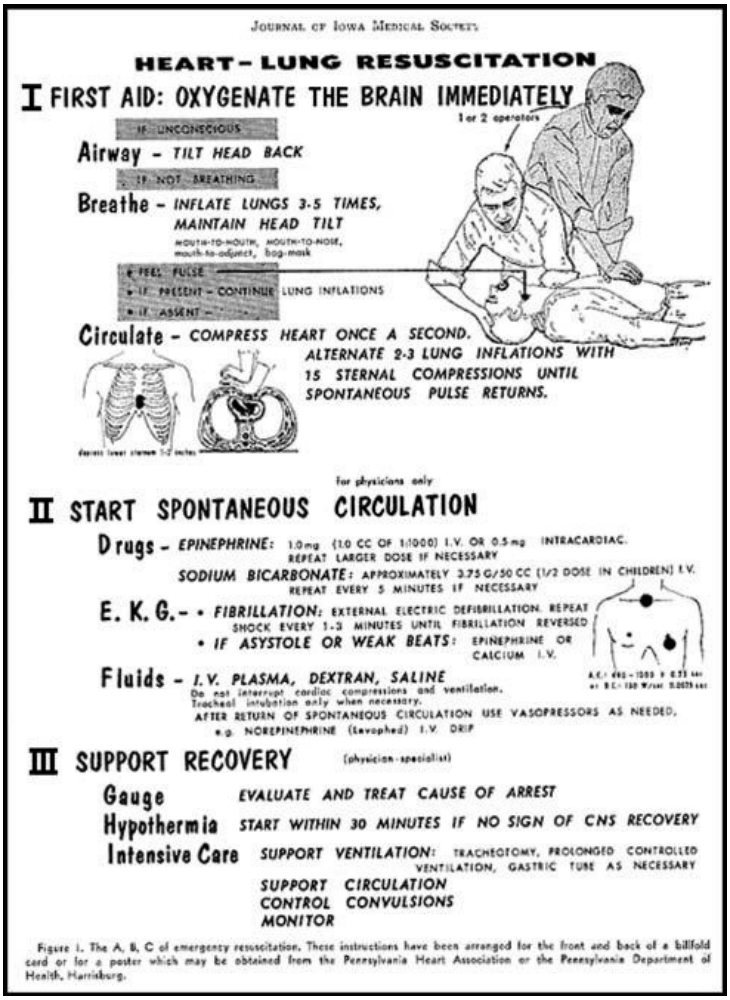


Figure 2. Peter Safar´s "first ABCs of resuscitation

Reprinted with permission, from Journal of the Iowa Medical Society [97]

However, the technique did not gain popularity since the application of moderate to deep rather than mild hypothermia for prolonged periods as well as practical management problems exhibited an increased rate of side effects in combination with indeterminate clinical outcome improvement. [98-100]

Even though interest in the technique was renewed in the 1980s by positive animal studies, no randomised controlled trials for the use of TH in cardiac arrest patients were published until 2001.[86,101] However, as early as 1993, Bernard and colleagues had started a prospective clinical trial to evaluate the effect of moderate hypothermia (33°C for 12 h) in comatose survivors of OHCA who compared to a retrospectively studied normothermic control group. They found a significant increase in survival with no increase in adverse events.[102]

1.3.1 Protective mechanisms of TH

The pathophysiology of hypoxic-ischemic and reperfusion injury in cardiac arrest is very complex and not fully understood.[24] However, a common denominator of the destructive cellular events is their temperature dependence.[87] The mechanisms by which therapeutic hypothermia exerts its protective effects on the different pathophysiological cascades, triggered by the circulatory arrest phase and the following reperfusion, are still subject to investigation. Figure 3 shows a schematic overview of TH-associated protective effects.[52,54,86,87]

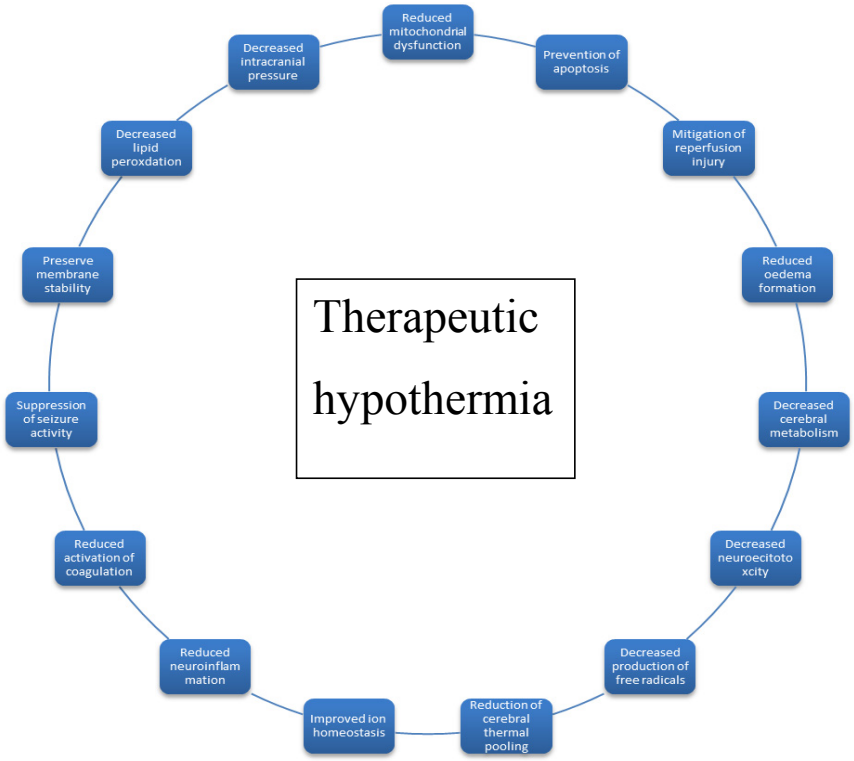


Figure 3. Protective mechanisms of hypothermia

1.3.2 Therapeutic hypothermia after cardiac arrest

In 2001, the first *randomised* trial was published by Hachimi-Idrissi and colleagues. It enrolled 30 unconscious non-VF-OHCA survivors in a cooling-helmet- feasibility study. The patients were cooled for 4 hours to 34°C and then passively rewarmed. Although the trial was underpowered to reach statistical significance with regard to outcome, it showed a favourable outcome in 13% of the hypothermia treated patients versus 0% in the normothermic group with no rise in complications. [103]

Then, in 2002, the New England Journal of Medicine published two RCTs on mild therapeutic hypothermia in comatose OHCA patients, one from Melbourne, Australia and one multicentre study from Europe.[82,83] The Australian trial included 77 comatose OHCA survivors. All cardiac arrests were of presumed cardiac origin with VF or non-

perfusing VT as first initial ECG-rhythm. The group treated with hypothermia was cooled to 34°C within 2 hours of ROSC and maintained at that temperature for 12 hours. Favourable neurological outcome was significantly more frequent in the hypothermia group (49%) than in the normothermic group (26%) at hospital discharge. Moreover, this trial also did not report significant side effects of the hypothermia treatment.[82]

The Hypothermia After Cardiac Arrest study (HACA) conducted in Europe enrolled 275 comatose OHCA survivors with cardiac-caused arrest and VF or non-perfusing VT as first initial ECG-rhythm. The hypothermia treated group was cooled to 32°C-34°C for 24 hours. Favourable neurological outcome was recorded in 55% in the TH group versus 39% in the normothermia group at six months after the cardiac arrest. The rate of complications for both groups did not differ significantly.[83]

The European and the Australian study involved a highly selected cluster of OHCA patients, including less than 10% of all assessed OHCA.[83] Exclusion criteria are depicted in table 1. Favourable neurological outcome of the initial randomized studies is depicted in figure 4.

HACA [83]	BERNARD ET AL. [82]
NON-VF/non-perfusing VT	NON-VF/non-perfusing VT
< 18 years, > 75 years	< 18 years, women < 50 years
> 60 min. to ROSC	No ROSC
Non-cardiac origin of arrest	Non-cardiac origin of arrest
Evidence of hypotension (MAP < 60mmHg > 30 min. after ROSC)	Cardiogenic shock (systolic BP < 90 mmHg despite epinephrine infusion)
Pregnancy	Women < 50 years
Response to verbal commands after ROSC	Not comatose after ROSC
Comatose state due to CNS depressive drugs prior due cardiac arrest	No ICU bed available
< 30°C at hospital admission	
Evidence of hypoxemia (arterial oxygen saturation < 85% > 15 min. after ROSC)	
Known coagulopathy	
Terminal illness	
Occurrence of cardiac arrest after arrival of emergency medical personnel	

ROSC- return of spontaneous circulation, ICU-intensive care unit

Table 1. Landmark studies **exclusion** criteria

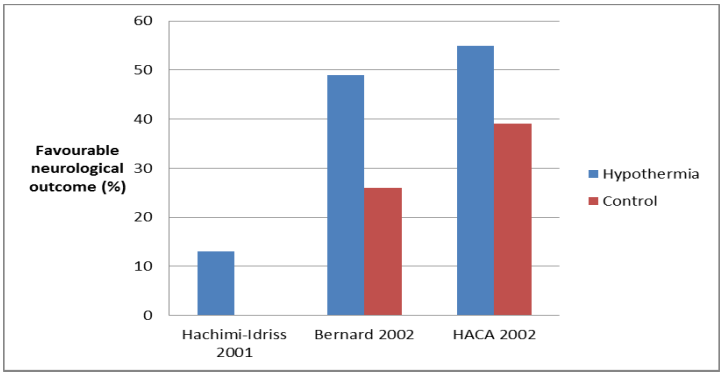


Figure 4. Randomized studies for TH after cardiac arrest. Favourable neurological outcome given as percentage at hospital discharge (Hachimi-Idrissi 2001 and Bernard 2002) and at six month (HACA 2002)

Following the publication of the Australian and European trials, ILCOR recommended the use of TH in comatose survivors after OHCA and that patients should be cooled to 32°C-34°C for 12-24 hours. Two randomized clinical trials supported the use in VF as initial ECG rhythm and one non-randomized, historical case-control study supported its use in other rhythm than VF/non-perfusing VT or in-hospital cardiac arrest.[84] For the patients treated with TH in the Australian study, cooling was initiated prehospitally by applying cold packs and continued after admission to the hospital with ice-packs over the head, neck, torso, and limbs. Target temperature was reached within 2 hours after ROSC.[82] The European study used an external cooling device that delivered cool air over the body and supplemented the hypothermia treatment with ice packs if necessary. Target temperature was reached after median 8 hours (interquartile range 4-16 hours).[83]

1.3.3 Application of TH

The increase of heat loss or the decrease of heat production achieves hypothermia. Mechanisms of heat loss include radiation, conduction, convection and evaporation and different cooling methods in post resuscitation care have been described (Table 2).[104] The age-dependent physiological response to a drop in core temperature is an increase in heat production by shivering which leads to an undesirable increase in metabolic rate and oxygen-consumption. Sedation and analgesia reduce the shivering threshold as well as shivering itself and seem to be crucial for TH-associated neuroprotection.[87]

Non-invasive	Invasive
Ice packs	Intravenous ice-cold saline
Forced cold air (fans, blankets)	Intravascular catheters
Cooling pads	Peritoneal, bladder, nasogastric cooling
Water-circulating blankets	Intra-aortic flush cooling
Cooling helmets	Extracorporeal circulation
Cold water immersion	
Transnasal evaporative cooling	
Antipyretic medication	

Table 2. Cooling techniques[87,105,106]

Phases of TH

The application of therapeutic hypothermia is usually divided into three segments: induction, maintenance and rewarming. The two landmark studies achieved target temperature within 2-8 hours in the majority of patients by external cooling.[82,83]

Whether early achievement of TH target temperature is beneficial for neurological outcome maintains a subject for debate. Animal data suggests that time to target temperature (TTT) is a predictor of good neurologic outcome and that intra-arrest cooling may even facilitate ROSC.[107-109]

Most guidelines advocate inducing TH as soon as possible and maintaining a temperature of 32°C-34°C for 12 -24 hours without major temperature fluctuations. The rate of rewarming should be 0, 25°C-0, 5°C/hour. [14]

Adverse effects

Hypothermia induces a wide array of physiological and pathophysiological changes. To what extent organ functions are altered depends upon the degree of hypothermia. Arrhythmia, shivering, haemodynamic instability, hypovolemia, ECG changes, coagulopathy, insulin resistance, pneumonia, electrolyte disorders, leukopenia, sepsis, renal failure, impaired bowel function, altered drug clearance, intracerebral bleeding, pancreatitis and pulmonary oedema are among potential complications associated with hypothermia.[52,86] TH mitigates cerebral damage after cardiac arrest.[86] The protective mechanisms not only amend the development of neurological injury, but also change the natural course of recovery of these patients. Moreover, TH in post resuscitation care necessitates active treatment with sedation, mechanical ventilation and sometimes muscle relaxation. Declines in drug clearance caused by hypothermia have been demonstrated for several commonly used ICU-drugs, e.g.: noradrenaline, adrenaline, opiates, midazolam, propofol, barbiturates, and muscle relaxants.[87]

1.4 Prognostication after cardiac arrest

Approximately 80% of OHCA survivors remain in a coma for variable spans of time and about two-thirds of patients will later die during their hospital stay, the majority due to neurological injury.[23,25] Persisting coma due to ischemic-anoxic encephalopathy is a severe condition and comas continuing for more than 3 days carry a risk of poor outcome of greater than 90 %. [110] After 1974, both traumatic and non-traumatic coma has usually been classified using the Glasgow-Coma-Score (GCS, Box 1.). [111]

Glasgow Coma Scale for Head Injury

Glasgow Coma Scale, Eye opening	
Spontaneous	4
To loud voice	3
To pain	2
None	1
Verbal response	
Oriented	5
Confused, disoriented	4
Inappropriate words	3
Incomprehensible sounds	2
None	1
Best motor response	
Obeys	6
Localizes	5
Withdraws (flexion)	4
Abnormal flexion posturing	3
Extension posturing	2
None	1

Box 1. Glasgow-Coma-Score (GCS), score is calculated by summoning all modules, range: minimum 3- maximum 15, lower score equals more significant neurologic dysfunction

For coma outcome, however, patients are commonly categorized in Glasgow-Pittsburgh Cerebral Performance Categories (CPC, Box 2.).[80]

Glasgow-Pittsburgh Cerebral Performance Categories

1. **Good cerebral performance**: conscious, alert, able to work, possibly mild neurological or psychological deficit.
2. **Moderate cerebral disability**: conscious, satisfactory cerebral function for independent activities of daily life or work in a sheltered milieu.
3. **Severe cerebral disability**: conscious, reliant on others for daily support, institutionalized or at home with extraordinary family effort, limited cognition. Varying from ambulatory condition to severe dementia and locked-in-syndrome.
4. **Coma, vegetative state**: Not conscious, no cognition, no interactions with environment.
5. **Death**: death by traditional criteria or brain death.

Box 2. Glasgow-Pittsburgh Cerebral Performance Categories modified after.[23]

Poor outcome after out-of-hospital cardiac arrest is usually defined as CPC > 2, describing states with total patient dependency. Since most patients would decide against a life with severe neurological disability and as health care for neurologically devastated individuals represents an enormous emotional, as well as socio-economic burden, the prospect of poor neurological outcome commonly initiates an assessment of adequacy to withdraw life support. [112,113]

In order to avoid “self-fulfilling prophecies” by early withdrawal on the one hand, and futile treatment on the other, reliable tests for cerebral prognostication with a false positive rate (FPR) of zero with narrow confidence intervals are warranted.

2. Objectives

2.1 Main goals

The overall objective of this thesis was to study the implementation of TH into daily practice, provide information on clinical management and outcome, and evaluate the application of TH in an age subgroup of OHCA patients not enrolled in earlier trials.

2.2 Secondary objectives

Paper I.

We implemented a simple cooling protocol in our ICU and applied simplified inclusion criteria to OHCA patients. The aim was to evaluate feasibility, effectiveness and safety of a simple cooling protocol based on the two landmark studies as well as to support implementation of therapeutic hypothermia.

Paper II.

With the introduction of TH to post resuscitation care, a wide variety of cooling methods and devices have become available. ICNs play a central role in the implementation and clinical management of TH, the aim of the study was to compare different cooling devices with regard to key nursing aspects.

Paper III.

The implications of TH on accuracy of cerebral prognostication were largely unknown. Our aim was to study the clinical practice of cerebral prognostication after OHCA in Norway after nation-wide implementation of therapeutic hypothermia.

Paper IV.

The HACA trial excluded OHCA patients older than 75 years, and there has been substantial debate about the application of TH in the oldest population. Our aim was to study outcome with TH in OHCA patients older than 75 years compared to younger patients.

3. Patients and methods

3.1 Background data

3.1.1 Setting and population

Stavanger University Hospital serves as the primary medical centre for 300.000 people and as a referral centre for approximately 400.000 people.[46,114] Paramedic-staffed ambulances cooperate with an emergency physician-staffed ambulance helicopter and rapid response car.[115] Unconscious survivors of OHCA are assessed by an intensive care physician and a cardiologist in the emergency department (ED) for possible percutaneous coronary intervention (PCI) and intensive care therapy. Traditionally, unconscious OHCA survivors not acting in response to verbal command and devoid of terminal sickness have been admitted to a 12-bed general ICU for supportive care and two days of mechanical ventilation before weaning[46]. Cardiopulmonary resuscitation and post resuscitation care is performed according to current European and Norwegian Resuscitation guidelines.[24,35,81,116] In 2002, we complemented our standard post resuscitation care with therapeutic hypothermia, using simple external cooling protocol of ice-water soaked towels over torso and limbs of the patient. During 2003, several commercial cooling devices were introduced in our ICU. In 2004, PCI availability was extended from daytime to 24-hour service.[114]

3.2 Study design

STUDY	TOPIC	DESIGN	STUDY POPULATION	STUDY PERIOD
1	Implementation of TH	Retrospective observational cohort study	Comatose OHCA patients	1/2001-12/2003
2	Nursing aspects of different cooling methods	Survey	ICU nurses	May 2005
3	Prognostication after OHCA	Survey	ICU Consultants	May 2005
4	Use of TH in advanced age	Retrospective observational cohort study	Comatose OHCA patients fulfilling the HACA inclusion criteria	6/2002-6/2008

TH-Therapeutic hypothermia, OHCA-Out-of-Hospital Cardiac Arrest, ICU-Intensive care unit, HACA-Hypothermia After Cardiac Arrest Study

Table 2. Study design

3.3 Data collection

3.3.1 Local clinical information management systems

The used prehospital cardiac arrest data was obtained from our local cardiac arrest registry based on the nationally approved Ustein template before they were anonymously transferred to the research study registry.[3] The Utstein registry was established in 1996 and was approved for scientific use by the Regional Ethics Committee, the Central Office for National Registration and the Norwegian Social Science Data Service.[46]

The hospital data variables were obtained from a national intensive care quality assurance database and local data related to the Northern Hypothermia Network. Most Norwegian ICUs gather data for quality assessment and resource management in a local database which exports data to the Norwegian Intensive Care Registry (NIR). The Norwegian Society of Anaesthesiology launched NIR in 1998 for mapping of Norwegian Intensive care activity and provision of quality assurance. NIR is one of the 36 national quality registries sanctioned by the National Data Security Council. Presently, 36 ICUs are reporting members of NIR.

The Northern Hypothermia Network (NHN) was established in 2004, is supported by the Scandinavian Critical Care Trial Group (SCCTG) and represents a clinical and research network. In order to report follow-up data to the Northern Hypothermia Network (NHN), we established a local registry. The local data collection had been approved by the Norwegian Social Science Data Service. The Regional Ethics Committee of Western Norway had issued a statement in which the use of such data was considered as quality assurance and waived the need for individual informed consent.

Surveys

The data for study II was collected during a 2-week period by means of an anonymous questionnaire filled out voluntarily by the ICNs employed in our ICU.

The data for study III was collected by a voluntary, anonymous and semi-structured interview containing six structured questions. Interviewed were the ICU consultants in charge of the 25 Norwegian ICUs of the NIR admitting cardiac arrest patients.

3.3.2 Ethics

The data used in study I and IV were core routine data collected for the ICU and NIR database. The collected data was intended for on-going quality control. The Regional Ethics Committee defined studies using such data as quality assurance research, and as no interventions were performed waived the need for informed consent.

The data for studies II and III were collected by a voluntary, anonymous survey, and a semi-structured telephone interview which served as local and national quality assurance research. None of the surveys involved patient contact or collected patient related information.

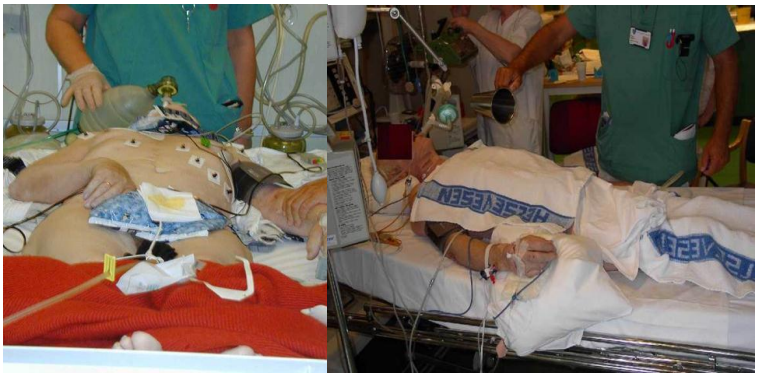
3.4 Data analysis and statistics

Statistical computations were done by using a spreadsheet program (Excel, Microsoft Corp., Redmond, WA) and statistical software (SPSS, SPSS Inc., Chicago, IL). The Mann-Whitney test was used for continuous variables and the chi-square test for categorical variables. Demographic data is presented as medians with either maximum and minimum values or interquartile range. In study II the Kruskal-Wallis-Test was used on ranked data. In study IV a multivariate logistic regression model and the Hosmer-and-Lemeshow-test for goodness of fit of the multivariate analysis were employed to analyse the data. A p-value of $\leq$ 0, 05 was considered statistically significant.

3.5 Methods

Paper I

Twenty-seven OHCA patients were treated with our simple external cooling protocol within 18 months after implementation of TH and compared with a historical control of 34 OHCA patients, fulfilling TH-inclusion criteria and treated within 18 months before implementation in our ICU. Inclusion criteria were: (i) no response to verbal stimuli after ROSC independent of initial rhythm and cause of arrest, (ii) absence of cardiogenic shock - defined as systolic blood pressure < 90mmHg despite of vasopressor/inotrope use, and (iii) age 18-80 years. Cooling was initiated in the field by paramedics with sport ice packs and continued in the ICU with ice-water soaked towels (Picture 1.). All patients were mechanically ventilated, sedated with fentanyl and midazolam, as well as paralysed with cis-atracurium to avoid shivering. Target temperature (32°C-34°C) was attempted for 12-24 hours before passive rewarming was allowed.



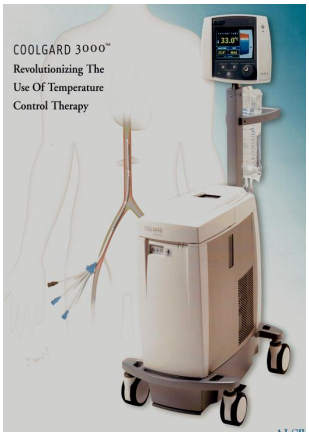
Picture 1. Simple cooling method

The temperature course of TH treated patients; Utstein template data, ICU-and hospital length of stay, adverse events during ICU stay, neurological outcome and survival to hospital discharge and 1-year survival were recorded. A Glasgow-Pittsburgh Cerebral Performance Category (CPC) greater than two defined poor outcome.

Paper II

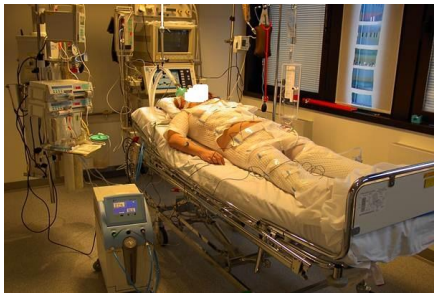
Several cooling methods have been described for therapeutic hypothermia treatment (Table 2.) and numerous commercial devices are available for application.

After implementation of a simple TH-protocol in our ICU in 2002 (Picture 1.), we introduced successively the CoolGard™3000 system (Alsius, Irvine, USA), the Thermowrap™ (MTRE, Yavne, Israel) and the ArticSun™ (Medivance, Louisville, USA) from 2003. All new devices were introduced by a group of "super-users" including physician and nursing staff. The CoolGard™ system is an invasive cooling method, using a central venous catheter (Cool Line® or ICY® catheter) that works as a heat exchanger (Picture 2.).[117]



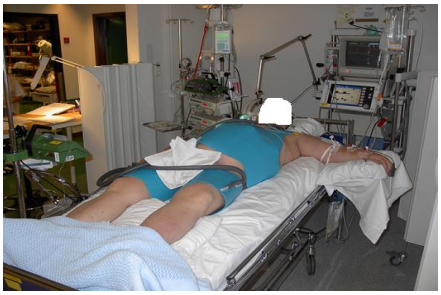
Picture 2. CoolGard™ and ICY® catheter (With permission of ZOLL)

The Thermowrap™ (Picture 3.) and the ArticSun™ (Picture 4.) are non-invasive systems, which apply cold circulating water by means of a suit or adhesive pads.[118,119]



Picture 3. Thermowrap™

(With permission of MTRE)



Picture 4. ArticSun™

(With permission of Medivance)

All commercial devices use a close-loop temperature control system. The aim of our study was to evaluate awareness and features of implementation of TH among nursing staff, as well as compare the four cooling techniques, that were simultaneously available at that time in our ICU regarding key nursing aspects: hygiene, noise level, work load, ease of application, and visual patient monitoring.

In May 2005, we delivered a structured anonymous survey (Box 2.) during a 2-week period in our 12-bed ICU, which we asked the nursing staff to complete.

Questionnaire

Number of years you have worked in the ICU……..

Number of cooling patients since 2002 < 3 , 3-5, 5-10, > 10

1. Did you understand the background for implementing therapeutic hypothermia (TH)? Y / N / Partly
2. Did you receive sufficient training in TH? Y / N
3. Were you sufficiently prepared when TH was introduced? Y /N /Partly
4. At the time of introduction, was there a written and sufficient cooling protocol in place? Y /N /Partly/Don t recall
5. How do you consider the cooling protocol now? Comprehensive and complete-acceptable-incomplete
6. Were you made aware of the potential complications? Y / N / Partly
7. Has there been sufficient information about potential complications? Y / N / Partly
8. Have you observed any problems related to TH yourself? No, if Y, what problems……..
9. Please list 3 potential complications with TH……
10. Is the collaboration between doctors and nurses good during treatment? Y/N/variable
11. Is it difficult with many different cooling techniques in use at the same time? Y/N/Partly
12. Please grade the 4 cooling techniques in use on a scale from 1-4 (1=worst and 4=best)

Method	Ease of application	Visual pat. monitoring	Work load	Hygiene	Noise level
Wet towels					
CoolGard™					
Thermowrap™					
ArticSun™					

Box 2. Questionnaire

Paper III

In the spring of 2005, we conducted a semi-structured telephone interview with consultants of ICUs listed in the Norwegian Intensive Care Registry (NIR) admitting cardiac arrest patients. Six structured questions were asked, including involved medical specialities, time of prognostication, the tests used, use of TH, presence of a standardized protocol for prognostication, as well as personal evaluation of predictive value of different tests (Box 3.).

Cerebral prognostication after out-of-hospital cardiac arrest

1. **At what time after the return of spontaneous circulation (ROSC) is cerebral prognostication performed?**

   first 24 hours 24-48 hours 48-72 hours after 3 days after 1 week

2. **Which medical specialties are involved in the prognostication of cardiac arrest survivors?**

   Anaesthesiologist Internal Med Neurologist Other _____ Multidisciplinary

3. **Which specific methods are applied for prognostication?**
   - Prehospital data (witnessed arrest, bystander CPR, initial ECG rhythm, no-flow time, CPR duration, prior health status)
   - Neurological examination Somatic somatosensory evoked potentials (SSEP)
   - Electroencephalogram (EEG) Biochemical markers Cranial computer tomography (CCT)
   - Magnetic resonance imaging Other_____

4. **According to you, which of the prognostic methods mentioned above has the greatest sensitivity/specificity?**
   - Prehospital data Neurological examination Somatic somatosensory evoked potentials (SSEP)
   - Electroencephalogram (EEG) Biochemical markers Cranial computer tomography (CCT)
   - Magnetic resonance imaging (MRI) Other_____

5. **Do you use a standardised protocol for cerebral prognostication after OHCA?**
   Yes No

6. **Do you use therapeutic hypothermia after OHCA in your ICU?**
   Yes No

Box 3. Cerebral prognostication survey

Paper IV

We retrospectively studied all adult OHCA patients who were treated with TH in our ICU from 2002-2008. Inclusion criteria were the same as in the HACA study with exception of the upper age limit: bystander-witnessed cardiac arrest, presumed cardiac origin of arrest, VF or nonperfusing VT as initial ECG-rhythm, collapse-to-ROSC interval less than 60 minutes, absence of symptoms of cardiogenic shock at hospital admission, collapse to ambulance arrival and start of CPR 5 to 15 minutes. Study endpoint was outcome at hospital discharge. Poor outcome was defined by Glasgow-Pittsburgh cerebral Performance category greater than two.

4. Results

4.1 Paper I

We identified 34 historic patients treated in our ICU within 18 months before the implementation of TH, who otherwise fulfilled the TH eligibility criteria. The implementation rate for TH was 100%, since all 27 patients eligible for the treatment received it. The simple cooling method required a median of 7, 5 hours to reach target temperature (TT) and was unable to obtain it in 11% of patients. TT was preserved for median 10 hours (6-19 hours) before passive rewarming, lasting median 10 hours (4-17 hours), was initiated. Rebound hyperthermia developed in 89% of TH treated patients. There was no statistical significant difference between the two groups regarding the Utstein template data, length of ICU or hospital stay. Seizures were significantly less, hypokalaemia and insulin resistance significantly more common in the TH treated group. Survival rates to hospital discharge were significantly better in the group of patients that received therapeutic hypothermia (59% vs. 32%, p=0, 05).

4.2 Paper II

Fifty-nine nurses (98% response rate) participated in the survey. They had a median of 7 years of ICU work experience and had been involved in a median 5 hypothermia treatments. All of the 59 nurses had worked with the ice-water soaked towels, the CoolGard™ and the ArticSun™-system. Only 25 (42%) had used the Thermowrap™-system in TH treatment. Ninety per cent of nurses felt they had good understanding of the background for TH, but merely 53% felt the initial training before was adequate and only 10% thought they were sufficiently prepared before the introduction of new methods. Seventy per cent felt partially prepared and 20% felt unprepared. With

regard to the existing cooling protocol only 20% answered that they thought it was comprehensive, whereas 70% of the nurses thought it was acceptable.

Considering the key nursing elements, we found significant difference between the different devices. The ice-water soaked towels came in second to the ArticSun™-system regarding ease of application, scored best in noise level and lowest in work load. The CoolGard™ and the ArticSun™-system achieved significantly better scores than the other methods. For visual monitoring of the patient, the CoolGard™ scored highest.

4.3 Paper III

The twenty-five participating hospitals represented all geographic regions of Norway. Ninety-six per cent were anaesthesiologist-led, but a multidisciplinary approach to prognostication was followed in 76% of ICUs. The majority of hospitals (72%) conducted cerebral prognostication 24-48 hours after patient admission, the remaining after 48-72 hours. Prognostic parameters applied were: Somatosensory evoked potentials (SSEP) (8%), biochemical markers (8%), magnetic resonance imaging (MRI) (8%), electroencephalogram (EEG) (52%), cranial computer tomography (CCT) (58%), prehospital data (76%), and neurological examination (100%). TH was used routinely in 80% of ICUs, still only one ICU used a standardized protocol for cerebral prognostication.

4.4 Paper IV

We included 113 adult patients treated with TH after OHCA in our ICU from 2002-2008 who fulfilled the HACA criteria with omission of the maximum upper age. Median age of the patients was 62 years (18-89 years), 77% were male, median time from collapse to ROSC was 15 minutes (3-50 minutes), bystander-CPR was performed in 76% and PCI in 63%. Overall good outcome was in achieved in 70% of

patients, and in 54% of patients older than 75 years. Collapse to ROSC time interval less than 15 minutes, age less than 62 years, applied bystander-CPR, and the time phase after implementation of the 2005 resuscitation guidelines were identified as independent predictors for good outcome in a multivariable analysis, whereas application of PCI and gender were not. Coronary angiography and PCI were performed significantly more frequent in patients under the age of 60 (74%, 35/47) than in patients aged older than 60 years (51% (34/66) (p=0, 02).

5. Discussion

A decade ago two randomized controlled clinical trials showed that lowering the core body temperature to 32°-34°C for 12-24 hours in comatose survivors of out-of-hospital cardiac arrest (OHCA) with ventricular fibrillation (VF) or non perfusing VT as initial ECG rhythm is associated with improved survival and neurological outcome. [82,83] The use of TH was recommended for comatose survivors after OHCA by the International Liaison Committee on Resuscitation (ILCOR) in 2003.[84] Many questions, however, regarding clinical management of TH after OHCA, risk of adverse events, timing, duration and method of cooling to be used, as well as the strength of presented evidence remained.

In June 2002, one year before ILCOR published its TH recommendations, we added a simple external cooling protocol to the neurointensive care of OHCA patients in our institution. Due to the ease of application and the low costs of the method, as well as the presence of a clinical protocol and preparation of both nursing and physician staff, we were able to include all eligible OHCA patients from day one. In contrast to other studies, we found that rapid implementation of a simple cooling protocol to achieve TH is feasible (paper I). Implementation has been slow in countries like the UK, Germany, Czech Republic, and the USA.[120-123] A recent American study reported utilization of TH in less than 1% of OHCA patients.[124] Although our protocol was not successful to reach target temperature in 11% of patients and rebound hyperthermia was common, we found the method safe, inexpensive and associated with improved outcome. Problems with overcooling using ice packs and cooling blankets, as reported by Merchant et al., were not encountered in our study.[125] The protocol used in our ICU did not burden the ICU or hospital budget since no additional purchase of medical equipment was necessary and the length of ICU and hospital stay was not prolonged. Storm and colleagues even proposed a significantly shortened time on mechanical ventilation and ICU stay for OHCA patients treated with TH.[126] The overall cost effectiveness of TH in OHCA is comparable to other

health care interventions, e.g. public access defibrillation, as hypothermia treatment only accounts for approximately 1% of the total costs generated by cardiac arrest patients. The bulk of costs (99%) is created by post hypothermia in-hospital and post discharge care.[127]

Despite compelling evidence on the outcome benefit of therapeutic hypothermia, implementation has been slow.[128] Several barriers to implementation of TH into clinical practice have been described: insufficient evidence, technical challenges, concerns about adverse events, increased work load/lack of resources, adherence to local practice patterns, poor leadership, poor attitude, and high costs. [120,121,123,129-131] After the two landmark studies showed reduced mortality and morbidity in VF-OHCA patients treated with TH, have numerous observational studies confirmed the beneficial results of TH.[54,82,83,132,133] Paper I was among the first studies published in this context.[24,54] Both, the 2005 and 2010 Resuscitation guidelines, a Cochrane report and a consensus report of five professional critical care societies have recommended TH in comatose OHCA survivors.[14,35,134,135] Still, there is some controversy regarding further evaluation of TH. [136] Nielsen et al. included 478 TH-treated OHCA patients in a meta-analysis and a trial sequential analysis and conclude that the data provided is inconclusive, associated with risks of systematic and random errors, that quality of evidence is low and that a larger randomized trial is needed. The same investigator is currently recruiting patients for the international target temperature management after cardiac arrest trial (ClinicalTrials.gov number NCT01020916) and plans to evaluate the effect of different target temperatures (33°C vs. 36°C) in 850 OHCA survivors.

Adverse events

Arrhythmia, haemodynamic instability, bleeding, pneumonia, electrolyte disorders, sepsis, renal failure, seizures, pancreatitis and pulmonary oedema are potential adverse effects associated with TH in post resuscitation care.[52] A recent review by Holzer reported a high rate of adverse effects in both the TH and the control group with 74% and 71% respectively. However, there was no statistical difference between the two groups.[137] Our study showed that hypokalaemia and insulin resistance were

significantly more common in the TH-treated group, whereas seizures were significantly more common in the normothermic group. The low incidence of seizure reported in our TH-cohort is most likely due to continuous muscle relaxation during therapeutic hypothermia treatment which was abandoned during the revision of our post resuscitation protocol in 2005. Induction of electrolyte disorders is common and important problem of TH as low levels of magnesium, potassium, calcium and phosphate can cause cardiac arrhythmias and episodes of hypotension.[104] Hypokalaemia is associated with the development of polymorph ventricular tachycardia and cautious potassium supplementation is advocated to maintain serum levels at approximately 3 mmol/l.[138] TH reduces insulin secretion and insulin sensitivity, frequently leading to hyperglycaemia.[104] As hyperglycaemia is associated with worse neurological outcome after cardiac arrest as well as an increased incidence of infection, renal failure and critical care neuropathy, tight glucose control with insulin infusion is recommended.[104,139] The registry-based study of 765 OHCA patients treated with TH by Nielsen et al. reported highest incidences of adverse events for pneumonia (48%), hyperglycaemia (37%), cardiac arrhythmia (tachycardia 34%, bradycardia 14%), hypophosphatemia (19%), hypokalaemia (18%), hypomagnesaemia (17%), and seizures (24%). Bleeding requiring transfusion (6%) and sepsis (4%) were uncommon.[140] The rates of adverse effects resemble those reported in our study results. A recent retrospective review by Mongardon and colleagues of 421 consecutive cardiac arrest patients, including 334 TH treated patients, confirmed a high incidence of infectious complications, especially pneumonia. Even though infections were more common in the TH group, they seem not to be associated with increased mortality.[141]

Technical difficulties

The time to achieve target temperature (TT) in our study was median 7,5 hours - approximately the same as in the HACA trial.[83] The clinical benefit of reaching TT rapidly after or even before ROSC is still under debate. Even though prehospital cooling has been shown to be feasible in numerous studies, it was not associated with

improvement in outcome.[142-144] Two registry-based studies of 986 and 452 TH treated OHCA survivors found no association of timing of TH and outcome.[145,146] A recent review on intra-arrest cooling (IATH) concludes that it seems to be safe and feasible, improves neurological outcome in animal cardiac arrest models when compared to normothermia or post-ROSC hypothermia, and to have some positive effect on ROSC rates and the reduction of cardiac function after ROSC. Data on the outcome benefit in humans is still limited.[147] Studies on the beneficial effects of TH on the myocardium propose increased myocardial salvage, reduced left-ventricular remodelling and decreased infarct seize, especially if TH is achieved before reperfusion.[148,149] There exists general agreement to reach TT quickly and this can easily be accomplished by undressing the patient, applying ice-packs and infusing ice-cold crystalloid.[86] Cardiogenic shock was initially describes as a contraindication for TH in the landmark studies.[82,83] We also applied this criterion as a contraindication for initiation of our TH protocol in our study (paper I). However, newer data suggests that TH might reduce mortality and provide circulatory support in acute cardiogenic shock.[148,150]

In order to maintain TH, non-invasive and invasive techniques are available (Table 2.). Our results of achieving stable maintenance TT with a simple cooling protocol concurs with other published data.[151] Several commercial cooling devices exist, but a „low-tech - no cost" approach with cold crystalloid infusions and ice-packs/ice-water-soaked towels is still feasible and might be especially appropriate for the community health setting with limited resources and a low OHCA-patient case load. In post resuscitation centres with higher case loads, however, the use of commercial devices has been widely accepted. The TH-cooling technique, as well as the commercial devices to be used, are commonly selected by doctors and then applied by ICU nurses. Toma et al. describes "interprofessional collaboration between nursing and physician staff" as a central element in the implementation process. Inconstant utilization of TH has been influenced by lacking awareness of the technique by the nursing staff and poor physician guidance.[129] The acceptance of critical care methods among ICU

nurses is often associated with the contentment of key nursing aspects, like ease of application and patient monitoring, hygiene, noise level, and work load.

In paper II we studied several available cooling appliances regarding core nursing elements. The conducted survey describes some interesting aspects of the different cooling methods and served as a quality assurance for our own implementation protocols. The ice-water soaked towels applied to torso and limbs were our original cooling method and scored high with regard to applicability and noise level. Even though hygiene and especially work load scored low, the simplicity and cost-effectiveness of this method makes it especially appropriate for hospitals with low case loads of post resuscitation patients. Nevertheless, this has to be balanced against the increased work load and possible hygienic problems.

All presented cooling methods are feasible for TH treatment after cardiac arrest.[117-119,151] Whether surface or core cooling is used, does not seem to influence outcome.[152] However, the target temperature of our TH treated patients could not be reached in 11% and 89% of patients in the TH group experienced rebound hyperthermia (paper I). Endovascular cooling appears to provide better control of temperature compared to surface cooling.[153] Furthermore, the CoolGard™ offered better visual monitoring of the patient and scored high in hygiene. These advantages have to be weighed against the invasiveness and high costs of the method. With regard to implementation, it seems that our nurses had a good understanding of and high degree of concurrence with TH. However, the high percentage of nurses dissatisfied with the protocol and their preparation prior to implementation were concerning and stress the importance of on-going efforts to educate and reassess newly introduced protocols.

The two landmark studies had numerous exclusion criteria (Table 1.), rejecting over 90% of assessed OHCAs.[82,83] The Hypothermia After Cardiac Arrest (HACA) study did not include patients older than 75 years and there is considerable debate whether the results can be extrapolated to this age group.[24,83] As the incidence of OHCA increases with age and as octogenarians represent the fastest growing segment of the elderly population in the industrialized world, the outcome benefit of TH in elderly

OHCA patients is of great relevance (paper IV). [20,154] The impact of age in OHCA has been evaluated in several studies and there exists a general consensus that old age influences post resuscitation mortality, but is not associated with universal unfavourable neurological outcome. [16,155,156] These results are confirmed in paper IV, where, although poor outcome was independently associated with older age, 54% of OHCA survivors older than 75 years achieved good outcome. Even more surprising, more than half of the patients over 80 years recovered to a cerebral performance category (CPC) 1 or 2. The Norwegian post resuscitation consensus statement expressed as early as 2004 that age should not be a factor for withholding PCI or TH treatment.[157]

Performance of bystander CPR and shorter time interval from collapse to ROSC are established predictors of good outcome.[16,158] Both parameters were also independent variables for good outcome in paper IV. The reported range for prevalence of bystander CPR in industrialized countries ranges from 8-55%.[159-161] The Stavanger region where we performed our retrospective cohort studies (paper I and IV) has rates of bystander CPR that are higher than reported.[162]

The time phase after implementation of the 2005 resuscitation guidelines was also independently associated with improved outcome in paper IV. The 2005 CPR guidelines focused on uninterrupted and effective chest compressions, normoventilation, 1-shock defibrillation strategy immediately pursued by chest compressions and a simplified compression to ventilation ratio of 30:2. [35,131] The positive impact of the 2005 guideline changes on outcome in our study concurs with results reported by Aufderheide et al. and Hinchey and colleagues.[163,164] The use of PCI did not reach statistical significance as an independent predictor of good outcome in paper IV, although several other studies have associated its use with improved outcome.[165-167] Although acute PCI treatment was usually reserved for ST-elevation myocardial infarction (STEMI), it might also benefit cardiac arrest patients with other ECG rhythms, given that chest pain and ST-elevation represent poor markers of acute coronary obstruction in OHCA patients.[24] Kern et al. suggest that ECG findings

should not be a decisive aspect whether or not to perform coronary angiography in the post ROSC period.[168] However, both patient selection and the rather small sample seize may explain the failure to separate PCI as an independent prognostic factor in paper IV. OHCA patients younger than 60 years were significantly more likely to receive coronary angiography/PCI than older patients according to our study results (paper IV). Even though age is neither an exclusion criteria for TH in the national consensus statement or in our local protocol, physician discretion is permitted and might have been a source of selection bias. The association between older age and underutilization of evidence-based therapy, including early invasive management and revascularization, has been recognized in previous studies.[169-171]

The combination of several therapies in post resuscitation care bundles, including early coronary angiography and PCI, TH, and hemodynamic support with inotropes and vasopressors was associated with improved outcome.[75,172] Modern post resuscitation care implies highly specialized care from different medical specialties. In accordance with trauma and stroke centers, the regionalization of post cardiac arrest patients seems to be related to improve outcome.[44,173] Longer prehospital transport intervals from triaging OHCA patients after ROSC directly to post resuscitation centers does not affect survival.[174]

Prognostication after cardiac arrest

In spite of advances in prehospital and hospital care, survival to discharge after OHCA has remained low in most areas with many survivors suffering from neurological sequelae.[160,175] Death, persistent coma, vegetative state or severe neurological disability rendering the patient reliant on daily support defines poor outcome after cardiac arrest.[23] Dependable prognostication of poor outcome is essential in order to avoid futile treatment and to reduce the emotional, as well as the financial burden on families and health care systems.[126,176] One could speculate that the changes in post resuscitation care with the introduction of TH and the transformed clinical course of OHCA survivors should mandate an increased vigilance in the prognostication approach. In early 2005, after nation-wide implementation of TH, we

conducted a survey to investigate if clinical prognostication patterns had changed along with altered post resuscitation therapy (paper III). In 2010, resuscitation guidelines acknowledged that among the most important developments since the 2005 ILCOR recommendations was the realization that the use of TH in post resuscitation management challenges many traditionally established prognostic parameters.[47]

Numerous parameters have been described in cerebral prognostication after cardiac arrest. However, few offer false predictive rates that approach zero and there exists only sparse data on the impact of TH on their accuracy. Cerebral prognostication had long been based on the work of Levy et al. from 1985, using an algorithm of brain stem reflexes, motor, verbal response and eye opening, as well as the duration of coma. [177] The 2000 resuscitation guidelines had not been updated at the time the survey was conducted and did not contain any specific information for the approach to prognostication after cardiac arrest.[178] In 2002, the Austrian Interdisciplinary Consensus Conference described 26 parameters that enable the clinician to make a prognostic assessment. However, only a GCS $\leq$ 5 or absent pupillary reflex at day 3, seizures at day 3-7 post ROSC, absent N20 somatosensory evoked potential (SSEP) response within 7 days post ROSC and a neuron-specific enolase (NSE) level > 33µg/ml were described to have a positive predictive value of 100% for poor outcome. [179] Predictive parameters with proven *insufficient* predictive value are: sex, age, cause of arrest, type of initial ECG-rhythm, initial Glasgow-Coma-Score, elevated body temperature, time interval of total arrest time, and the duration of CPR.[112,180]

The 2005 ERC guidelines state that laboratory analyses like NSE, S-100β, base deficit, glucose level or soluble P-selectin do not represent reliable prognostic parameters. Somatosensory evoked potentials (SSEP) measured at 72 hours after ROSC have 100% specificity for poor outcome and that the use of electroencephalography (EEG) performed 24-48 hours after arrest can be helpful in prognosis assessment.[35] The 2005 American Heart Association (AHA) guidelines for post resuscitation care state that no single predictor can reliable prognosticate poor

outcome. Further, an EEG performed 24-48 hours after ROSC is described as "useful predictive information". As reliable predictors for poor outcome, somatosensory evoked potentials (SSEP) measured 72 hours after ROSC and 5 clinical signs are given.[181]

The clinical signs to predict unfavorable outcome or death are:

- *At 24 hours* after ROSC: absent corneal reflex, absent pupillary reflex, absent withdrawal to pain, no motor response
- *At 72 hours* after ROSC: no motor response

In lack of a clinical applicable prognostic post resuscitation algorithm issued by the major resuscitation organizations, the American Academy of Neurology issued a decision algorithm in 2006 based on parameters (brain stem reflexes, early myoclonic status epilepticus, SSEP, NSE, motor response) with FPR of zero with narrow confidence intervals (CI) tested on day 1-3 after cardiac arrest. Major confounding factors for the application of this algorithm contain shock, residual sedation, residual muscle relaxation, renal or hepatic failure and use of therapeutic hypothermia.[180]

Timing of prognostication

There exists a general consensus that prognostic accuracy improves with time after the onset of coma.[110] Traditionally, the majority of comatose OHCA survivors usually emerged within 3 days, and all with good neurological outcome did so within 2 weeks.[182] Moreover, delay to day three accounts for the unreliability of brain stem reflexes and the GCS – the mainstay of neurological examination-within the first 48 hours. [183,184] All of the ICUs in our survey conducted prognostication within 72 hours, the majority even within 24-48 hours. This practice yields the potential danger of rash limitation or withdrawal of care and the inclination of self-fulfilling prophecies. Furthermore, 80% of surveyed ICUs used TH routinely. The effect of therapeutic hypothermia on traditional predictive parameters has not been amply evaluated and therefore caution is warranted when these are used to found a limit-or-withdraw –care

decision in TH treated patients. Surprisingly, an American study from 2012, found a similar pattern of early assignment of poor prognosis and possibly premature withdrawal of care within 72 hours post cardiac arrest in their TH treated OHCA cohort. [185]

Prognostic parameters

A multimodal approach increases the prognostic accuracy and all of the surveyed ICUs (paper III) relied on more than one prognostic parameter for their decision to limit or withdraw care.[180] The most frequently applied parameter was clinical neurologic examination. This predictive variable has been extensively studied and validated as a parameter for comatose OHCA survivors. In lack of confounding factors, like use of hypothermia, muscle relaxants, large doses of sedatives, as well as the presence of organ dysfunction and shock, neurological evaluation represents a reliable factor of prognostication.[180] A recent study by Rossetti et al. validated the 2006 American Academy of Neurology prognostication algorithm and found that clinical neurological examination 36- 72 hours post ROSC was unreliable. The documented false predicted rates (FPR) for unfavourable outcome were significantly higher than reported in the algorithm: $\geq$ 1 absent brain stem reflexes (4% vs. 0%), early myoclonus status epilepticus (3% vs. 0%), and motor response less than flexion (24% vs. 0%).[186] Status epilepticus in post resuscitation patients who received TH treatment is associated with a FPR of 7-11, 5 % for poor outcome. [187,188]

Unexpectedly, the second most frequent parameter used in our study was prehospital data. Even though several of these parameters are associated with unfavourable functional outcome, their high FPR prohibit accurate dichotomization between good and poor outcome. [180] The international resuscitation guidelines describe prehospital data as unreliable predictors for prognostication. [24,47,131]

Studies on the predictive value of cranial computer tomography (CCT) and magnetic resonance imaging (MRI) in anoxic-ischemic coma have associated several findings with poor outcome. Their role in prognostication, however, remains undetermined due

to the small number of studied patients, wide variety of tested parameters and timing of examinations. [24,47] CCT was used in over half of surveyed ICUs, whereas MRI only played a minor role. CCT was rated as having minor importance in prognostication according to the interviewed consultants, but its use is suggested in exclusion of structural causes of coma.[24] Even though MRI is superior to CCT in demonstrating cerebral lesions after global hypoxic-ischemic events, the lack of evidence and the potentials hazards of transporting a critical ill patient to the MRI lab challenge its use in prognostication after cardiac arrest. [24]

Electroencephalography (EEG) has been comprehensively evaluated as a prognostic predictor after cardiac arrest and a meta-analysis showed a FPR of 3% (95%CI 0, 9-11%) for malignant pattern within 72 hours post ROSC in patients not treated with TH.[180] It was used in over half of all surveyed ICUs (paper III). According to current guidelines are EEG results alone not suited to predict futility.[24,47] However, in absence of confounding factors, Rosetti et al. presented FPRs of zero for unreactive EEG background activity in TH treated OHCA patients.[186]

Somatosensory evoked potentials (SSEP) are less susceptible to metabolic disorders or drugs than EEG.[189] The absence of the bilateral N20 response in comatose survivors *not* treated with TH 24 hours after ROSC predicted poor outcome with FPR 0, 7 (95%CI 0, 1-3, 7%) and their use is encouraged by international resuscitation guidelines.[24,47,180] Our study, however, showed that SSEP was applied in only two surveyed ICUs and was not regarded as an important technique in cerebral prognostication. Lack of awareness, limited accessibility, as well as lack of experience with this test might be possible explanations. SSEP seem to be a reliable predictor also in TH treated patients with FPR of 0%.[186,190] However, Leithner et al. reported a FPR of 3% for SSEP recorded later than 24 hours post ROSC. Two TH treated OHCA patients of this study, presented absent SSEP 72 hours after ROSC and still made a good recovery. [191]

Several biochemicals such as neuron-specific enolase (NSE), S100β, neurofilament protein and creatine kinase brain isoenzyme (CK-BB) have been investigated for

outcome prediction after cardiac arrest but played only a minor role in our study (paper III). A systemic review associated NSE levels > 33ug/L within 24 hours after ROSC to invariably poor outcome, whereas studies on S100β, CK-BB and neurofilament protein showed poor prognostic ability.[180] Data on the predictive accuracy of NSE in patients treated with TH has shown conflicting results. [192-195]

Additionally, assays for these markers are not commonly available in many countries, including Norway. Current resuscitation guidelines do not support the sole use of biomarkers to evaluate outcome in post cardiac survivors and several studies have reported. [24,47]

The current resuscitation guidelines suggest a combination of predictive modalities should be used in TH treated OHCA patients since every single prognostic test had FPRs greater than zero reported. Absent N20 SSEP response or unreactive background on EEG at 36-72 hours after admission, as well as lack of pupillary and corneal reflex > 72 hours post ROSC are regarded as accurate parameters, whereas biomarkers were marked as adjunctive. Status epilepticus and motor response less than flexion are considered unreliable signs for prognostication.[47]

6. Main findings

Paper I

Rapid implementation of therapeutic hypothermia with a simple external cooling protocol was feasible in 100% of eligible patients. It was safe, added no extra costs and almost doubled survival to hospital discharge compared to a historic control group. Safety or cost concerns need not be a barrier for implementation of TH.

Paper II

The evaluated cooling methods differed significantly with regard to key nursing aspects. Simple external cooling methods are still feasible and might be especially appropriate for smaller hospitals with low OHCA case loads.

Paper III

Despite the high (80%) use of therapeutic hypothermia, most Norwegian ICUs performed prognostication early in the post resuscitation phase and founded decisions on mainly neurological examination, prehospital data, CCT and EEG findings. Somatosensory evoked potentials were underused, whereas predictive accuracy of prehospital data, CCT and EEG appears overrated.

Paper IV

Although age affects outcome in cardiac arrest, comatose survivors older than 75 years had good outcome in more than 50% of cases. Limitation of post cardiac arrest care should not be based on age alone.

7. Limitations of the studies

Paper I: The retrospective, single centre study design and small patient population limit the extent of conclusion that can be drawn from this study. Physician bias for exclusion of OHCA patients for TH treatment was possible. The temperature course of the normothermic patient group was not available.

Paper II: Single centre study with a small number of participants with limited numbers of cooling procedures. Not all nurses had worked with all cooling devices.

Paper III: Only one physician per hospital was interviewed during the survey and thus the collected data might not represent the general practice at the institution. The study has limited international validity as only Norwegian ICUs were included. No information was made available whether the timing of prognostication impacted decisions to limit active treatment.

Paper IV: Non-randomized cohort design in a single centre with a short follow-up interval. Patient selection bias for both PCI and/or TH treatment was possible. Data on co-morbidities and baseline health status were not available for the multivariate analysis. The group of patients studied only constitutes a small portion of all assessed OHCA and thus extrapolation of our results to other subgroups of elderly OHCA patients, like non-witnessed or non-shockable arrests might not be appropriate.

8. Future aspects

In order to transform new evidence into daily clinical practice and support rapid, wide-spread implementation, the academic bodies of resuscitation could consider to incorporate more detailed, but user-friendly protocols in the resuscitation updates, combined with a time schedule in which implementation of the evidence should be completed.

The optimal cooling method, benefit of intra-arrest cooling, velocity of induction, duration and rewarming rate are still undetermined. Data on the role of ICNs as key players in the implementation process and in the practical application of TH is still rare. Many questions remain about the optimal temperature management of cardiac arrest patients. The published data support a target temperature of 32°-34°C for 12-24 hours, however, the optimal temperature range, possibly individualized for every patient, has not been determined.

The 2 landmark studies evaluated only a small portion of OHCAs and in order to establish the benefit of TH in other subgroups of cardiac arrest further studies are warranted.

More data are required about timing and accuracy of established prognostic parameters in comatose OHCA patients treated with TH.

9. Erratum

Paper IV

The abstract of paper 4 states incorrectly bystander CPR as an inclusion criteria for the HACA study.

The Wilcoxon`s rank test was not applied in the data analysis of this paper.

Merely the p-value for the difference of the use of PCI for patients older and younger than 60 years was given. Patients younger than 60 years (35/47) received PCI significantly more frequent than patients older than 60 years (34/66). The figures given, depict the numbers of patients younger (47/113) and older than 60 years (66/113).

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