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Post Cardiac Arrest Care

*Evaluation of prognostic tools, Patient outcomes and
Relatives' experiences at 6 months after the event*

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Abstract

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The overall aim of the present thesis was to study post-resuscitation care of cardiac arrest (CA) patients treated with target temperature management 33°C with a focus on evaluation of two prognostic tools: variations in cerebral venous saturation and acute magnetic resonance imaging (MRI) findings on the brain post-CA. An additional aim was to investigate patients' neurological outcome and relatives' experiences 6 months after the event. *Paper I* describes the cerebral oxygen saturation of blood obtained from a jugular bulb (SjvO₂) catheter. The results showed that patients with poor outcome tended to have higher SjvO₂ values, but this difference was only significant at 96 and 108 hours post-CA. The main findings of *Paper II* were that patients with good outcome displayed a pathological pattern mainly in the frontal and parietal lobes on MRI of the brain. Patients with poor outcome had an extensive pathological pattern in several brain regions. Furthermore, very low apparent diffusion coefficient (ADC) values were associated with poor outcome regardless of brain region. *Paper III* investigated physical and cognitive function over time, between one month and 6 months post-CA, as well as life satisfaction at 6 months. The results showed that impairment in physical and cognitive function is common in CA survivors but tends to decrease over time. Despite a severe illness, which has impaired the physical and cognitive functions, satisfaction with life as a whole was reported by 70% of CA survivors. In *Paper IV*, relatives described their experiences 6 months after a significant others CA. The analysis resulted in three themes reflecting relatives' everyday life 6 months after the event: Difficulties managing a changed life situation, Feeling like I come second and Feeling new hope for the future. In *conclusion*, the results of the present thesis have increased our understanding of the two prognostic tools that were investigated; they have generated new and revealed aspects that should be taken into account during prognostication and assessing neurological outcome of this group of patients. The thesis has also shown that the healthcare needs to improve its routines for follow-ups and information provision to both patients and their relatives.

Keywords: cardiac arrest, hypothermia, neurological outcome, cerebral oxygenation, MRI, relatives

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Memento Vivere

List of Papers

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

- I Wallin, E., Larsson, IM, Nordmark-Grass, J., Rosenqvist I., Kristofferzon ML., Rubertsson S., (2015) The prognostic value of using a jugular bulb catheter for measuring oxygen saturation in patients treated with target temperature management 33°C after cardiac arrest: a prospective study (*Submitted*).
- II Wallin E., Larsson IM. Kristofferzon ML., Rubertsson S., Larsson EM., Raininko R. (2015) Acute brain lesions on MRI in relation to neurological outcome 6 months after cardiac arrest treated with hypothermia (*manuscript*).
- III Wallin E., Larsson IM. Rubertsson S., Kristofferzon ML. (2013) Cardiac arrest and hypothermia treatment-function and life satisfaction among survivors in the first 6 months. *Resuscitation*, 85: 538-543.
- IV Wallin E., Larsson IM. Rubertsson S., Kristofferzon ML. (2013) Relatives' experiences of everyday life six months after hypothermia treatment of a significant other's cardiac arrest. *Journal of Clinical Nursing*, 22 (11-12): 1639-46.

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Abbreviations

ADL	Activities in daily life
BI	Barthel Index
CA	Cardiac arrest
CPC	Cerebral Performance Categories
CT	Computed tomography
ECG	Electrocardiogram
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
ICU	Intensive Care Unit
IHCA	In Hospital Cardiac arrest
LiSat	Life satisfaction
MAP	Mean arterial pressure
MMSE	Mini mental state examination
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
OEF _b	Oxygen extraction of the brain
OHCA	Out of Hospital Cardiac arrest
PCI	Percutaneous Cardiac Interventions
PEA	Pulseless Electric Activity
PTSD	Post-traumatic Stress Disorder
QoL	Quality of life
ROSC	Return of Spontaneous Circulation
RLS 85	Reaction Level Scale
SaO ₂	Arterial oxygen saturation
ScvO ₂	Central venous oxygen saturation
SjvO ₂	Jugular bulb vein saturation
SvO ₂	Venous oxygen saturation
SSEP	SomatoSensory Evoked Potential
TH	Therapeutic Hypothermia
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Introduction

Cardiac arrest (CA) is a common cause of mortality in the Western world¹ and is defined as “the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness and apnoea (or agonal, gasping respirations)”.² Despite progress in the research and improved treatment, the overall survival rate is low. As a critical care nurse in the intensive care unit (ICU), it is a challenge to care for post-CA patients due to their complex and unsure prognosis. The challenge is to find tools that can be used in most intensive care units, and that are reliable and suitable for their purpose. It is also important to increase knowledge about neurological outcome and relatives’ experiences. The present thesis will focus on prognostication for CA patients admitted to the ICU, patients’ neurological outcome and relatives’ experiences.

“It is in the beginning of December and the year’s first snow falls. Sixty-five year-old Sven collapses while shovelling snow, something his wife notices while she looking out of the window. She runs out to Sven who does not respond when she calls his name. She runs back to the house and calls the emergency medical services (EMS), which guide her through performing cardiopulmonary resuscitation (CPR) over the telephone. When the EMS arrives, they continue with CPR and Sven regains circulation after approximately 18 minutes from the telephone call. When Sven arrives at the emergency ward, he is unconscious and has gasping respiration. He is intubated and ventilated and coronary angiography is performed before he arrives at the ICU. Later Sven’s family arrives to the ICU knowing that the situation is serious and uncertain. They receive verbal information about the CA and about treatment with therapeutic hypothermia (TH), which will continue for 24 hours. They are told that the neurological impact and outcome cannot be determined before three days post-CA. During the time at the ICU Sven is monitored and several neurological investigations are performed. Three weeks later Sven is discharged from the medical ward, but he is weak physically and his family notes that he functions different mentally. “

Background

Cardiac arrest

The mechanisms underlying CA are numerous and can be divided into cardiac and non-cardiac causes.³ CAs are categorized as occurring in-hospital CA (IHCA) and out-of-hospital CA (OHCA).^{2,4} The Utstein Style was published in 1991 and defined the “Chain of survival” concept: *Early access – Early CPR – Early Defibrillation – Post-resuscitation care*. The aim was to treat and report the incidence, treatment and outcome of OHCA² and IHCA in a uniform way.⁴ Despite these guidelines, accurate documentation of resuscitation time is difficult because of the psychological stress and intensive work required during resuscitation attempts.⁵ It may also be difficult to compare studies due to unclear presentations of the study population, such as inclusion and exclusion criteria, as well as lacking information on what criteria the decision to resuscitate is based.¹ When several of these factors are imprecise, the result is major variation when reporting the incidence and outcome of CA.¹

Survival after cardiac arrest

Approximately 275.000 OHCA occur annually in Europe and in Sweden the reported rate is 5 000-10 000 OHCA annually.^{6,7} The overall survival rate from CA is still low,⁸ but during the last decade the survival rate at one month has increased from 5% to 10% for OHCA treated by the EMS.^{6,7} Factors affecting increased chance of survival depend on the initial ECG rhythm, delay to arrival of the EMS, place of arrest, witnessed status, bystander CPR and age⁸ as well as the use of telephone-guided CPR, increased access to public access automated defibrillators, and post-CA care in hospital.^{3,7} These factors are based on the chain-of-survival concept.⁹ During the past decade, the knowledge on post-resuscitation care has increased, and such care includes TH, in-hospital, particularly ICU care and coronary angiography including percutaneous coronary intervention.^{3,5,10}

Figures for the incidence of IHCA in Europe varies between 1-5 events/1000 hospital admission as well as survival to hospital discharge vary between 6.6-42% due to the different inclusion criteria and do-not-resuscitate policies that are used.¹¹⁻¹⁴ Similar numbers is presented by from Sweden.⁷ Patients with IHCA present a challenge to the medical professions

and research evaluation owing to their comorbid conditions and the reason for the hospital stay.⁴ A recently published study from Norway showed that IHCA patients were older, had a higher proportions of witnessed CA, bystander CPR, early defibrillation and professional first rescuer compared to the OHCA group.¹⁴

Post-cardiac arrest syndrome

For CA patients who regain ROSC, the ischemic event affects the entire body. Post-cardiac arrest syndrome is often used as a collective term to describe the pathologic state occurring post-CA.¹⁵⁻¹⁷ It is primarily characterized by a global ischemia-reperfusion phenomenon with a nonspecific activation of the systemic inflammatory response and affects all organs.¹⁷ Post-cardiac arrest syndrome is complex and can be described as a state of shock, high fever, and severe biological disorders, a similar reaction to that observed during sepsis.^{15,17} Severity varies with the cause of the CA, the severity of the ischemic insult and the patient's health before the CA. A short time to ROSC is known to reduce the risk for post-cardiac arrest syndrome.¹⁶ Post-cardiac arrest syndrome occurs during the period from the first 20 minutes after ROSC to 72 hours post-CA, and it is mainly during this period that interventions and treatments are initiated.¹⁸ The ischemia-reperfusion injury probably continues longer but the exact time is not defined. The term post-cardiac arrest syndrome refers to: *myocardial dysfunction, systemic ischemia/reperfusion response, persistent unresolved pathological process and brain injury*.^{16,18}

The myocardial dysfunctions post-CA is transient and full recovery may occur. Impaired contractile function, variable diastolic dysfunction and decreased work capacity are problems that are mentioned and that causes severe systolic dysfunctions and is also the second factor most likely to cause death post-CA.¹⁹ Even in cases of rapid improvement in contractile function, vasopressors and fluid infusions are maintained until 72 hours post-CA.¹⁷ When ROSC is achieved, it leads to whole body-ischemia and reperfusion injury, which is a major concern in post-CA patients.¹⁹ This causes an oxygen debt leading to generalized activation of immunological and coagulation pathways, which increases the risk of multiple organ failure and infection.

Persistent pathologic processes refer to various causes of CA, such as pulmonary diseases, haemorrhage, sepsis or intoxications that, complicate the situation and the post-cardiac arrest syndrome.

Brain injury

The brain has a high metabolic demand, is vulnerable and has limited tolerance of ischemia. Ischemia can briefly be defined as a reduction in cerebral blood flow to a critical threshold at which brain injury occurs.²⁰ The CA exposes the brain to global ischemia that affects the whole brain, in contrast to traumatic brain injury or stroke where focal ischemia is more common.²⁰ The brain areas most sensitive to ischemia are the grey matter of the brain, hippocampus, the front and parietal lobe, the thalamus and the basal ganglia.²¹⁻²³ Brain injury caused by asphyxia is the most common cause of morbidity and mortality in post-CA patients.^{16, 17, 24-28}

The affected areas of the brain can explain neurological and clinical symptoms when assessing prognosis. Information about any brain injury is important to pass on to the patients' families,²⁸ as brain injury may affect quality of life for patients and their families²¹

Brain injuries are caused by several mechanisms, such as interruption of blood flow, free radical formation, disordered calcium homeostasis, activation of cell death and pathological cascades and excitotoxicity.^{18, 28} The progress and the severity of these factors vary with the duration of ischemia, the extent of tissues damage, oxygen concentration, temperature and pH.¹⁹ The failure of cerebral microcirculation can be caused by a prolonged time to ROSC despite adequate cerebral perfusion pressure and lead to persistent ischemia and infarctions in some brain regions.¹⁶ Animal studies have shown that perfusion defects appear in 5 minutes and increase as the period of ischemia is in process.^{29, 30}

Cerebral circulation remains impaired despite ROSC, and a short period of hyperaemia are replaced by a period of hypoperfusion.^{29, 31} Slow recovery has been observed mainly in the diencephalon, mesencephalon and cerebellum in pigs post-CA.³¹ After ROSC, the autoregulation of the brain is affected i.e. becomes dependent on the mean arterial pressure (MAP). Cerebral blood flow, the cerebral metabolic rate of oxygen consumption and glucose consumption decrease and the cerebral vascular resistance increases during the period 24-48 hours post-CA and are to be corrected within 72 hours.^{16, 17}

Other factors that can impact brain injury post-CA are fever, hyperglycaemia and seizures.³²

Treatment after cardiac arrest

The two goals of treatment and care post-CA are first initial treatment of shock and organ failures and, second optimization of cerebral protection.

The care is time sensitive, occurs both out of hospital and in hospital and is often affected by a variety of medical components. The treatment is therefore complex and comprises caring for patients ranging from stable survi-

vors to unstable comatose patients with a pathology that affects treatment and outcome.

Therapy protocols adapted for post-CA care have been shown to improve survival and are recommended.³³⁻³⁵ The protocol should focus on general critical care measures, such as blood glucose control, and include specific interventions intended for care of post-CA patients. These include goal-directed therapy regarding ventilation, support for circulation, consideration of coronary angiography and neuroprotection therapy, where TH is recommended.^{24, 26} Besides use of TH post-CA, different neuroprotective treatments to influence neuronal cell death, oxygen free radicals and to improve cerebral haemodynamics have been tested, mainly in experimental studies.³⁶ Various pharmacological treatments have been studied, such as thiopental,³⁷ calcium-entry blockers³⁸ and adenosine³⁹ but have not shown the same benefits as TH.⁴⁰ In a recent study neurostimulants such as methylphenidate and amantadine were used to stimulate reawakening in comatose post-CA patients and considered as a promising treatment, but need to be further evaluated.⁴¹ Other neuroprotective measurements that have been shown to be important are optimizing the cerebral perfusion,^{26, 42, 43} fever management,^{44,}⁴⁵ hyperglycaemia management⁴⁶ and seizure control.⁴⁰

Ventilation and oxygenation

It is commonly to use 100% oxygen during resuscitation and also when ROSC is achieved. Use of hyperoxia has been shown to be associated with increased in-hospital mortality compared with use of normoxia and is now being questioned and debated.⁴⁷⁻⁵⁰ Hypoxia during the early stages of reperfusion harms postischaemic neurons by causing excessive oxidative stress.^{51,}⁵² Based on current knowledge fraction inspired oxygen (FiO₂) should be administered to produce an arterial oxygen saturation of 94-96%.⁵³

Another important aspect of ventilation management is the level of carbon dioxide (PCO₂). Patients are commonly hyperventilated during and after ROSC with a high respiratory rate, despite the recommendations of 10 breathe per minute.^{24, 54} During TH the metabolic rate and in parallel oxygen consumption and production of PCO₂ decrease. This means that ventilator settings need to be adjusted to avoid hyperventilation. Hyperventilation decreases cardiac output³⁵ and may induce cerebral ischemia.⁵⁵ Likewise hypocarbia causes cerebral vasoconstriction³⁵ and may derange the cerebral perfusion as well as limit the benefits from TH. According to current knowledge and guidelines, ventilation should be adjusted to achieve normal PCO₂ and should be monitored through regular measurement of arterial blood gas values.^{35, 56, 57} Blood gas values are temperature dependent. The most common analysis measuring blood gases is the alpha-stat management that measure blood samples at 37°C regardless of the patients actual core temperature. When using the alpha-stat management the interpretation of

PO₂ and PCO₂ may be overestimated and pH underestimated. The alternative is pH-stat management, which corrected blood samples of patients actual temperature.⁵⁸ Which method to use is not settled in the care of post-CA care and TH. Regardless of whether method that are used the effect of temperature should be taken into account.⁵⁸

Circulation

Haemodynamic instability is common post-CA and may be one cause of poor prognosis. Stabilization of circulation involves fluid therapy, administration of vasoactive drugs and consideration of mechanical support i.e., intra-aortic balloon pump. It is expected that patients will receive fluid approximately 3.5-6.5 liters intravenous crystalloids fluid during the first 24 hours post-CA to achieve the desired pressure and resulting in a positive fluid balance. The most common cause of OHCA in adults is acute coronary syndrome. Therefore the use of coronary angiography should be considered and immediate coronary revascularization in OHCA patients is recommended.^{16, 59}

The current guidelines do not recommend any targets in haemodynamics values today but a target mean arterial blood pressure (MAP) of 65 to 100 mmHg is mentioned.³⁵ To treat myocardial dysfunction and ventricular dysfunction post-resuscitation, the vasoactive drugs commonly used in cases of acute heart failure are used. Over aggressive treatment of haemodynamics values with arterial hypertension and evaluated systematic blood flow may result in brain swelling and intracranial hypertension. Adverse neurological outcome has been described among patients with higher MAP and cardiac index during TH,⁶⁰ but whether this is a cause or a sign of severe brain damage is not known. Use of mechanical circulatory support is an expanding treatment but clinical evidence is limited owing to logistics and the limited number of therapy beds available today.¹⁷

Therapeutic hypothermia

Hypothermia is known to have neuroprotective effects that comprise several factors such as reduced cerebral metabolism and slowing of the excitotoxic cascade.⁶¹⁻⁶⁴ The cerebral metabolism is reduced by between 5% and 7% for every decreased degree of body temperature.⁶⁴ Hypothermia in clinical trials was used in the 1950s in patients with traumatic brain injury and CA. In these trials, relatively deep hypothermia was used (30°C or lower).⁶⁴ The trials were discontinued owing to the severe side effects and uncertain benefit of the treatment. In the early 1980s, animal studies and uncontrolled clinical trials following CPR showed that benefits could be obtained with mild hypothermia (32-35°C). When mild hypothermia was used fewer severe side effects were observed.⁶⁴

In 2002, two randomized controlled studies demonstrated that TH treatment, during 12-24 hours after CA improved survival and neurological outcomes among patients admitted to hospital after OHCA.^{65, 66} Hypothermia is considered to mitigate the pathophysiological cerebral changes that occur during the post-CA period and to influence metabolism, cerebral blood flow, inflammatory response and neuro excitatory pathways.⁵⁸ Therefore, TH is now a recommended treatment in post-CA patients to reduce neurological impairment and increase survival.^{24, 26, 65, 66}

The practical approaches to TH are divided into three phases: induction, maintenance and rewarming. Each phase, though mainly induction and rewarming, requires close monitoring of the patient by the ICU team. This is because TH have several physical side effects and if they remain untreated the positive effects of TH may be suppressed.⁶⁷ Induction of TH can easily be conducted using cold (4°C) intravenous fluids (30-40ml/kg), but this need to be complemented with other methods and both invasive and non-invasive methods have been described.⁶⁸⁻⁷³ The maintenance phase requires effective temperature monitoring to avoid temperature fluctuations, regardless of methods. The optimal rate of rewarming is not known, but the current recommendation is to rewarm at a rate of about 0.25-0.5°C/hours.⁵⁹ Evidence for the ideal method, duration and target temperature is still inconclusive.

Recently, the Target Temperature Management study group showed no improvement in outcome in post-CA when a body temperature of 36°C was used compared to 33°C.⁷⁴ Nonetheless international guidelines have not changed their recommendations regarding ideal target temperature. Based on current knowledge, it would seem to be important for the medical team treating post-CA patients to be trained in a chosen method that suits its logistical situation. Starting hypothermia in the pre-hospital setting has been investigated in several studies, but as yet no improvement in outcome has been shown.^{75, 76}

Withdrawal of therapy

Today it is possible to offer elective and emergency treatment to an increasingly elderly and morbid patient population owing to improvements in medical and technical skills in healthcare. For some critically ill patients, treatment may prolong suffering instead of helping them return to life and regain health and an acceptable quality of life. These issues constitute the background of development of the Swedish Society of Anaesthesia and Intensive Care national guidelines for treatment strategies for life support in the ICU.⁷⁷ The guidelines are intended to assist the intensive care physician in selecting an optimal treatment for patients with life-threatening conditions.⁷⁷

Medical and ethical limitations such as withdrawal of medical treatment and refraining from cardiopulmonary resuscitation are decisions that occur

in the healthcare.⁷⁸ Before these decisions are made there are several factors to be considered.⁷⁷ Besides the medical aspects there are ethical principles, such as beneficence, non-maleficence, autonomy, and justice that should be considered in resuscitation care.^{77, 79, 80}

A sudden CA is unexpected and often associated with an acute and stressful situation for all persons involved. The patient's desires and or medical history are not always known when the CA occurs. In the acute situation, it is the healthcare personnel who decide when to start and when to stop resuscitation care.⁷⁹ No definitions exist that specify how long resuscitation should be continued, meaning that each case should be assessed individually.^{79, 81} This is a complex situation and the decision to proceed with or withdraw life-sustaining treatment cannot only be based on caregivers' personal conviction,⁷⁹ which may lead to death and become a self-fulfilling prophecy.^{27, 79}

The intensive care and treatment should be prioritized based on the function and prognosis of all vital organs, which determines whether active treatment is required or should be continued.^{77, 82, 83}

The decision should also be systematically discussed with all persons involved in the situation including the patient's family. If possible the patient's desires should also be considered.^{77, 79, 83} In Swedish hospitals, only a small proportion of patients are actually included in the decision to not resuscitate,⁸⁴ meaning that the patient's autonomy is not taken into account. The reasons given for this are that physicians do not think that patients should be involved and that they are uncertain about involving the patients in the decision.⁸⁴ On the other hand, patients desire an open and honest discussion about their diagnosis and prognosis, and therefore think it is natural to talk about possible limitations in life.⁸⁵ Many patients also reported wanting a family member and a nurse to participate in the conversation.⁸⁵

Relatives may have been present during the dramatic OHCA event and may also have performed basic life support. They should therefore be given the opportunity to be present during the resuscitation care in hospital as well as in the decision to proceed with or withdraw life-sustaining treatment.^{77, 79, 86, 87}

Prognostication

Prognostication and prediction of outcome in post-CA patients are challenging and complex for clinicians and require extensive knowledge of CA, hypothermia and the physical changes that occur post-CA. The hypothermia-induced changes and the impact of sedatives on the metabolism may influence the time to recovery of the brain and assessment of outcome.^{67, 88, 89}

Neurological recovery follows a specific pattern involving seven phases, from cranial nerve reflexes to slight or no disability.⁹⁰ Time to awaking after CA and TH is highly variable and often longer than three days.⁹¹ Early

awakening with intentional movements is associated with a good recovery.⁹¹ The prognosis is generally poor for patients who remain in coma >4 days post-CA.^{91, 92} However some patients may recover later due to a residual effect of sedative drugs and/or more severe ischemic insult, and current guidelines recommend that prognostication should not be performed until 72 hours after rewarming.⁸³

Today there is no single accepted method for predicting CA-patients outcome. Therefore it is recommended that several methods be used in combination in the prediction of poor outcome, i.e. a multimodal approach as well as to evaluating each patient individually.^{83, 93} Methods recommended are: repeated neurological examination by experienced neurologists as well as neurophysiological examinations, biochemical markers in peripheral blood and neuroimaging.^{26, 83}

Neurological examination

In the ICU, the daily bedside neurological evaluation is a part of the clinical and neurological examination, but may be affected by sedation and is therefore difficult to interpret.⁹³ Neurological examination including corneal reflexes, pupillary reflexes and motor response is a part of the prognostic evaluation.⁹⁴ It can be performed early when normal core temperature has been achieved but needs to be repeated, as reliability is poor during the early phase after ROSC.⁹⁵ The absence of pupillary light response or corneal reflexes 72 hours post-CA have been found to be unreliable predictors of poor outcome in post-CA patients treated with TH.⁹⁵

Neurophysiological examination

There are two main neurophysiological examinations that are relevant in the neurological evaluation post-CA; somatosensory evoked potentials (SSEP) and electroencephalography (EEG)

Examination using SSEP is recommended in the prognostication guidelines because it is less affected by temperature and use of sedation.^{96, 97} However, the examination may show higher reliability in patients with normal core temperature.^{96, 97} The SSEP is a small electrical signal that can be recorded noninvasively from the skull by stimulating one of the peripheral nerves using a set of electrical stimuli. In CA patients the median nerve is most commonly stimulated bilaterally at the wrist.⁹⁸ In a well-performed SSEP, cortical responses have to be absent bilaterally to predict poor outcome,⁹⁹ but the decision to withdrawal therapy should not be based on the SSEP response alone.¹⁰⁰ The advantage of SSEP is that a neurophysiologist assistant can perform it at the ICU; the disadvantage is that opportunities to use of SSEP outside larger hospitals are limited.

EEG is another neurophysiological test that has been shown to be a useful method and that adds valuable information for multimodal prognostication

in comatose CA-patients treated with TH.^{101, 102} It is considered a complex method and expertise is required to interpret the data. The accessibility, technology and interpretation of EEG may be a barrier to use of the method outside the larger hospitals. Using a simplified amplitude-integrated EEG monitoring (aEEG) enables the ICU nursing staff to apply the EEG when the patient arrives at the ICU. It is also possible to evaluate continuously and sufficient for the neurophysiologist to evaluate and guide therapy, to providing prognostic information.^{101, 102}

Biochemical markers

There is a theoretical advantage to use biochemical markers, which are quantifiable biological substances often measured in peripheral blood. They are easy to sample, give a quantitative result and are likely independent of the effects of sedative drugs. The most studied biomarker of brain injury in CA patients is neuron-specific enolase (NSE) and S-100.¹⁰³ New biomarkers, such as glial fibrillary acid protein (GFAP) and procalcitonin have been investigated.⁹⁸ Using GFAP in CA patients treated with TH has not been shown to have sufficient sensitivity to predict neurological outcome after CA. Both NSE and S100B were more sensitive assessments in this area.¹⁰⁴ A single high test should be handle with care; analysing trends of biomarkers might be more useful than looking at a single value.⁹³ Hypothermia and sedation may affect the results but differences in laboratory methods and a lack of standardization may also do so. Before any biomarker can be included in common guidelines and achieve general use, more trials evaluating biomarkers are needed.

Cerebral saturation

The human brain requires optimal oxygenation to maintain tissue function and is dependent on adequate arterial oxygenation and blood flow.¹⁰⁵ During and because of CA, global cerebral ischemia occurs due to a drop in oxygen delivery to the brain. Decreased blood flow is one of the factors that affecting neurological injury and outcome during CA and post-CA. Cerebral blood flow during manual CPR is insufficient and generates a flow this amounts to 10-40% of normal.¹⁰⁶ After ROSC cerebral blood flow continues to be impaired until 24-72 hours post-CA.^{107, 108} Cerebral blood flow after ROSC is characterized by four phases; multifocal no-reflow, transient global hyperaemia lasting 15-30 min, hypoperfusion and after 24 hours secondary hyperaemia were blood flow and metabolism are restored.¹⁰⁹ By measuring blood flow or oxygen consumption using arteriovenous differences in oxygen, a haemometabolic variable is created that enables assessment of whether or not blood flow or oxygen consumption is adequate.¹⁰⁵

Regarding measurement or monitoring of cerebral oxygen during CPR and in the post-resuscitation period, both noninvasive and invasive methods are described. Using near infrared spectroscopy provides regional cerebral saturation values and indicates the real-time balance between cerebral oxygen supply and demand in the frontal lobe during CPR¹¹⁰ and during the post-resuscitation period.^{111, 112} Using a catheter in the jugular bulb vein to measure venous oxygen saturation (SjvO₂) is an invasive method that requires accurate placement of the tip of the catheter in the jugular bulb.⁴⁹ Measurements can be performed intermittently or continuously. The method is used more extensively in the care of patients with head injuries and during cardiovascular surgery to optimize cerebral blood flow.¹¹³⁻¹¹⁵ It has also been used as a supplement to post-resuscitation care.^{107, 108, 116} Jugular bulb saturation monitoring ought to provide early signs of brain ischemia caused by hypotension and hypoxia and indicate adequate treatment. The range of normal values of SjvO₂ is considered to be 55-75%.^{114, 116} SjvO₂ values ≤50% in SjvO₂ indicate higher extraction of oxygen and are thought to reflect cerebral ischemia; SjvO₂ values ≥80% reflect underlying hyperaemia or luxury perfusion¹¹⁷ and may imply that blood is passing through a metabolically inactive brain.¹¹⁸ Therapeutic hypothermia has been shown to increase values by lowering the metabolic rate¹¹⁹ but more studies are needed before SjvO₂ measurements can be introduced in clinical practice.

Neuroimaging

Neuroimaging in the clinical setting may be valuable and can provide insight into brain pathophysiology post-CA.¹²⁰ Computed tomography (CT) and magnetic resonance imaging (MRI) have mainly been used to improve the knowledge of the anatomical structures of the brain. Other imaging techniques are Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), which seem promising but are limited by small sample sizes and also lack of comparison with standard methods of prognostication. A few studies also report conventional cerebral angiography and near infrared spectroscopy. These studies are also limited by the small sample sizes and lack of comparison with standard methods of prognostication.¹²¹

Computed tomography

CT is the first method, which could depict the brain with clear cross-sections images revealing grey and white matter, liquid-filled cavities and many pathological changes. It was a breakthrough for neuroscience and is now an established method for imaging for all organs in the body.¹²²

The first CT was developed and installed in a hospital in England at the beginning of the 1970s. The two investigators received the Nobel Prize in Medicine and Physiology in 1979.^{122, 123} Studies using CT post-CA have

found that a loss of differentiation between grey and white matter can be seen within 24 hours post-CA and is more common in patients with poor outcome.¹²⁴⁻¹²⁷ Current studies using CT imaging to predict outcome in CA survivors are mainly small, with variable timing of imaging, retrospective and case studies, and have level of specificity that is too low to be used alone in the prognostication.^{121 124-127} The current guidelines do not recommend CT imaging for prognostication post-CA, as there is now a more sensitive method, MRI to visualize post-anoxic brain injury.²⁴ However a CT of the brain can be used to rule out intra cranial haemorrhages caused by CA or when trauma to the head or neck is suspected.⁹³

Magnetic resonance imaging

Nuclear magnetic resonance (NMR) has been used in chemistry since 1940's. The method could be used in imaging after discovering how to encode the position-dependent information in the MR signal in 1973. The first images using the technique in the brain of patients were taken in the 1980's and thereafter, medical use and further development of MRI have been rapid. In 2003, two investigators received the Nobel Prize in Medicine and Physiology for discovering and developing the basic technique in the area of MRI.¹²⁸

The MRI scanner contains both a strong magnetic field, a powerful computer and components that send and receive radio-frequency pulses.¹²⁹ There is several safety factors taken into consideration before an MRI is performed.¹²⁹ The patient lies inside the scanner in a tunnel, approximately 2 metres long and 60 centimetres wide, the scanner is about 2 metres high and 2.5 metres long: the size, design and capacity may differs due to the a constant development of the MRI technology.¹²⁹ Physical symptoms such as anxiety and panic are reported among patients undergoing MRI: these symptoms may require treatment in order to make the examination feasible.^{130, 131}

The simplified principle of MRI is based on a strong magnetic field and radio waves with no harmful radiation.¹²⁸ MR signal can be produced with many nuclei but hydrogen nuclei (protons) are used in routine medical imaging because the hydrogen is the most abundant atom in the body and provides a strong MR signal.¹²⁸ The protons act as "small magnets" when inserted into a strong magnetic field. The protons absorb energy and emit detectable signals when they are exposed to radiofrequency pulses from a transmitting coil.¹³² A receiver coil is placed closed to the examined organ to detect the signals emitted by excited protons in the tissue. To locate the signal spatially in three dimensions, magnet gradients are used i.e. linear changes have been produced in the magnetic field strength.^{129, 132} Gradients are switched on and off during the collection of the imaging data, and this switching creates a loud hammering noise. Excitation of the protons can be

made with different radio frequency pulses and emitted signals can be collected in different time points after the excitation. These entities are called sequences. The durations of imaging sequences varies and are usually some minutes. The duration of a total examination of one patient depends on types and numbers of sequences.¹³² It is most often between 30 and 60 minutes.

MRI is very sensitive to small changes in tissues, both between normal anatomical structures and between normal and pathological areas. Different details can be seen with different sequences. Therefore one examination is composed of images obtained by several sequences and images are routinely taken or produced in more than one plane.

MR method is based on the motion of protons. How much signal can be produced in tissue depends on the number of protons (proton density) and how freely they can move. The signal intensity i.e. brightness in images depends on that and is always influenced by many factors but one of them is dominant; f. e. if the proton density is the dominant factor the images are called proton density-weighted. The time in which the protons return to the equilibrium after excitation with a radio frequency pulse is called a relaxation time. The relaxation time has two components: longitudinal and transversal. The longitudinal component is called T1 relaxation time and the transversal component T2 relaxation time. If one of the relaxation times is the dominant factor the images are called T1-weighted or T2-weighted. One type of the commonly used sequences is diffusion-weighted imaging (DWI) in which the imaging sequence is sensitized to motion on a molecular level. DWI primarily reflects the proton mobility in the extracellular water. If DW images have been obtained at least in three planes and with two so called b-values (gradient factors) it is possible to calculate an apparent diffusion coefficient (ADC) which is a measure of diffusion across an area of tissue per second.¹³² The results can be shown as ADC maps (Fig.1).

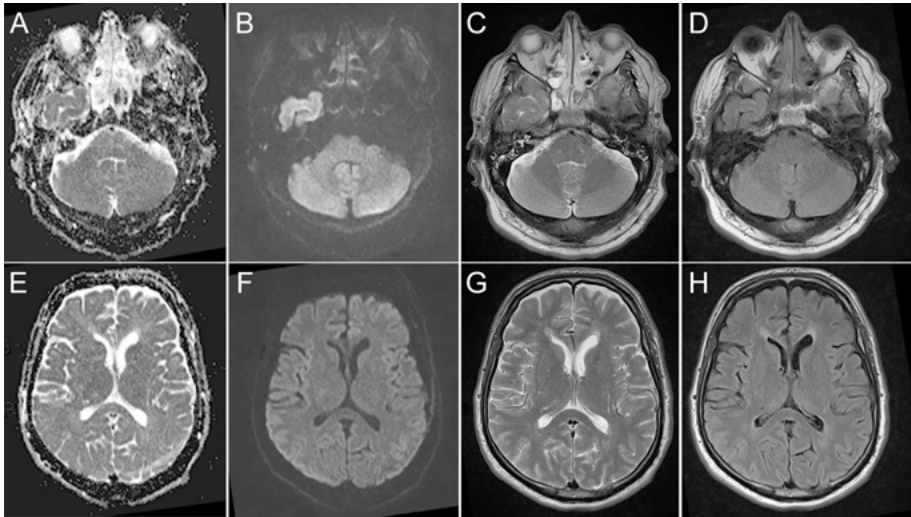


Figure 1. Examples of MRI with axial slices through the cerebellum (upper row) and the ventricular level in the cerebrum (lower row) using an ADC map (A, E), DWI (B, F), a T2- weighted spin echo (SE) sequence (C, G) and a T2- weighted fluid-attenuated inversion recovery (FLAIR) sequence (D, H). Examination 100 hours after 35 min CA (asystole) in a 65-year old man surviving with a good outcome. No abnormalities were detected on MRI.

MRI has come to be more commonly used when investigating and evaluating ischemic changes post-CA and seems to be promising as part of the prognostication.⁹⁸ Several MRI findings have been shown to be associated with poor outcome, such as low grey matter and hippocampal volume, global cerebral atrophy and acute ischemic lesions to the parietal and occipital cortices.

DWI is a highly sensitive method to reveal acute hypoxic/ischemic lesions and to differentiate acute and older lesions by distinction of intracellular (cytotoxic) and extra cellular (vasogenic) oedema. In acute hypoxic/ischemic lesions, cytotoxic oedema causes a secondary reduction of extracellular space, which leads to restricted mobility of water molecules i.e. restricted diffusion. Diffusion restriction is seen as high signal intensity on DWI and dark areas on the ADC maps.^{132, 133}

In small-scale studies, MRI using DWI within 3-5 days post-CA has shown to be sensitive to ischemic injuries and cytotoxic oedema and has been related to neurological outcomes¹³⁴⁻¹³⁷ Still the clinical value of MRI is limited due to the small retrospective studies.¹²¹

Outcome after cardiac arrest

Survival after CA is described as survival after resuscitation, survival after discharge from hospital or long-term survival.⁴ The purpose of resuscitation

and subsequent TH is to regain the patients' pre-CA status. Survival has mainly been reported and defined in relation to disease-specific short-term outcomes such as ROSC to neurological outcome at 90 days using Cerebral Performance Category¹³⁸ (CPC) scale or a modified Rankin scale¹³⁹ (mRS), depending on the trial size.¹⁴⁰

In recent years, interest in and awareness of long-term outcomes including quality of life (QoL) and cognitive function have increased. A consensus between an overall neurocognitive assessment and quality-of-life-assessment should be considered when reporting outcome in post-CA patients.¹⁴⁰ This also requires increased knowledge of specific follow-ups for patients who have been critically ill, CA survivors and their relatives.

Critical care and Critical illness

The routine for patients who remains unconscious after ROSC, post-CA is to be monitored and cared for in the ICU.

Scandinavian anaesthesiologists have been the initiators of intensive care and in Sweden the first ICU was established in Borås in 1952.¹⁴¹ One major reason for ICU developments was the polio epidemic that resulted in respiratory failure among the victims as well as a need for monitoring of vital signs.¹⁴² Historically ICU care has been provided in isolation from patients' primary care, and the ICU environment affects both the person who has a critical illness and their relatives. The ICU is a technical environment where care and treatments are focused on organ-specific issues with less focus on functional impairments.^{143, 144} Patients are continuously monitored and closely observed by the ICU team, which includes doctors, nurses and physiotherapists. The reason for ICU admission is failure of one or more organs and is often associated with a serious life-threatening situation. Patients are often neurologically compromised due to sickness and medical reasons, and the situation may prevent the patient from actively participating in the decision and treatment process. It is common for critically ill patients to have no or few memories from the ICU, and some patients have memories of unreal experiences of the ICU.¹⁴⁵

After ICU and hospital discharge, persons who have been critically ill, including CA survivors, experience physical, cognitive and mental health impairments associated with reduced QoL. Life after critical illness and CA survival is affected by and described as entailing severe fatigue, feelings of anxiety and/or depression, increased dependency in activity of daily life (ADL) and decreased QoL.¹⁴⁶⁻¹⁵⁰

The relatives must assume increased responsibility as decision-makers during critical illness and later for recounting the experiences of the ICU for the patients and are thereby exposed to stress and anxiety. This implies that former ICU patients and CA survivors will need support and assistance from

the people around them at discharge, which places heavy demands on the family and entails change in relatives' QoL.^{146, 151-154}

Neurological outcome

The CPC scale was initially designed to estimate the functioning of patients with traumatic brain injury¹³⁸ and measure the primary outcome. In recent years, the CPC scale has been questioned as a tool for assessing patients' physical and psychological functions and for its inability to assess patients' QoL and cognitive functioning post-CA.^{155, 156} The CPC scale ranges from 1-5, where 1 represents good cerebral performance and 5 represents death. The scale is usually dichotomized into good or poor outcome, where CPC 1-2 corresponds to good outcome and CPC 3-5 to poor outcome.

An alternative scale is the mRS scale, which provides more information on functional domains but it is less validated for use in the post-CA care.^{139, 157} The scale was introduced in Scotland in 1957 and is used to estimate disability or dependence in ADL in people suffering from stroke.^{139, 158} The scale ranges from 0-6, where 0 represents full recovery and 6 represents death. Good outcome in mRS has been defined as 0-3 when it is assessed in the post-CA care.^{159, 160} The different levels of function in the CPC and mRS scale are presented in Table 1.

Table 1. *Cerebral Performance Categories (CPC) scale and modified Rankin scale (mRS).*

CPC score	Function level	mRS score	Function level
		0	No symptoms
CPC 1	Good cerebral performance. Able to work and lead a normal life	1	No significant disability. Able to carry out all usual activities, despite some symptoms.
CPC 2	Moderate cerebral performance. Able to work part-time	2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
CPC 3	Severe cerebral disability. Dependent on other for daily support.	3	Moderate disability. Requires some help, but able to walk unassisted.
CPC 4	Coma or vegetative state. Unaware of surrounding, no cognition	4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
CPC 5	Death	5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
		6	Death

Physical function

During ICU care and critical illness, patients are immobilized which leads to muscle weakness that lasts from months to years after discharge from hospital.¹⁶¹ This weakness may impact on patients' physical functions and ADL as well as lead to mental health problems.¹⁶² Early mobilization at the ICU has been shown to be feasible and safe and may increase patients' ability to regain muscle strength,^{162, 163} resulting in a reduced length of stay in the ICU, lowering hospital healthcare costs and an increased ability among patients to an independent life.¹⁶²

It is common for CA survivors to describe feelings of fatigue that may decrease their physical activity.^{147, 150} Surviving a CA may affect life and results in uncertainty and doubt about one's own ability. This may be reinforced by a decrease in physical strength and a sense of decreased physical control. Patients with medical illness report that areas of great importance

are basic domains of activity such as walking and self-care, participation and environmental factors and that when these goals were met function were improved.^{144, 164} Activities that are part of daily life, such as dressing and daily hygiene, must be performed regularly if one is to live independently and many CA survivors find this cumbersome.¹⁴⁷ If restrictions in ADL exist this can lead to uncertainty about physical efforts and develop into a more conservative lifestyle and ultimately passivity.

Cognitive function

An important long-term complication of critical illness and critical care is cognitive impairment that occurs irrespective of the cause of critical illness.¹⁴⁶ The term cognitive function includes a variety of functions, such as attention, verbal/non-verbal memory, executive function, languages, mood and motor skills. It is difficult to define cognitive impairments and to reach a consensus, and therefore there is great variation, with studies reporting an incidence between 4-65% and an association with reduced QoL.¹⁴⁶ Impairments are also variable during the year after discharge, and rates of between 9-70% are reported, implying that cognitive impairments are common, often severe and appear to be permanent.¹⁶⁵ Cognitive impairment often becomes apparent after ICU discharge and affects people of all ages following critical illness.¹⁴⁶

Cognitive impairment are also found in CA survivors due to critical illness, as is the hypoxic brain injury caused by the CA²¹. Similar variation exists: this is mainly due to unclear follow-up times and the different instruments used for identifying impairments.^{148, 166} Ratings of the degree of cognitive impairment range from mild to severe; cognitive impairment affects both the individual and those closest to him/her to varying degrees.⁸³ Among CA survivors, impairment primarily concern memory, attention, executive and perceptual functions.^{83, 167} Recovery from cognitive dysfunction caused from critical illness and critical care is often slow, and its outcome is difficult to predict. Cognitive rehabilitation is more common among patients with brain injury, but is rarely used in patients with general critical illness.¹⁶⁵ Even if rehabilitation will lead to full recovery, patients can improve their functioning through the use of adaptive strategies.¹⁶⁵ Existing studies in the area are small observational studies that have used different instruments and follow-up times making it difficult to compare results and generalize.

Measuring health

Life satisfaction

Life satisfaction is a subjective well-being concept and can be defined as contentment, harmony or even happiness.^{168, 169} Satisfaction with life is dependent on the present state and is based on a comparison with a standard that each individual sets for him or her self.¹⁶⁹ The level can change depending on individuals' ability to adapt to a new situation. It is a contested concept and has been used in rehabilitation care as a measure of how successful an individual's coping process is and how satisfied he/she is with life.¹⁷⁰ The purpose of using the concept is to mobilize the resources of individuals with impairment(s) by having realistic goals that may allow achievement of optimal life satisfaction.¹⁶⁸ Positive predictors of satisfaction with life in a survey of the Swedish population were: higher educational level, good financial situation, and being employed.¹⁷⁰

Quality of life

Quality of life is a broad and complex measure of the individual's own assessment of their physical, mental and social wellbeing. WHO's holistic definition of QoL is considered to have credibility and reads as follows: "the individuals' perception of their position in life in the context of the culture and value system and in relation to their goals, expectations, standards and concerns. It incorporates in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of the environment".¹⁷¹ Interest in and awareness of QoL have increased among CA survivors.

Relatives' experiences of critical care and critical illness

Relatives of critically ill persons have stressful memories from the ICU that can affect them and cause symptoms of anxiety, depression, sleep disturbances, sadness and fear.^{152, 153, 172-174} The machines and monitoring devices make relatives feel overwhelmed, and they want to receive information about the different parameters to feel confident in the ICU environment.¹⁷⁵ Some relatives develop post-traumatic stress disorder (PTSD), and the risk of illness for family members increases with the seriousness of the crisis.^{154, 176, 177} Furthermore female gender, length of ICU stay, lower educational levels and family members' symptoms of depression and anxiety before the patient's ICU stay are factors that have been shown to be associated with higher levels of stress.^{178, 179}

Relatives of an ICU patient need constant, clear and honest information if they are to feel hope, even if the prognosis is poor, and be able to cope with feelings of chock, anxiety and depression.^{154, 180-184}

Feeling that there is hope is important part for relatives regardless of the seriousness of the illness and relationship to the patient.^{185, 186} Hope for families of a critically ill person may entail being able to be physically present at the ICU, having reassurance that their family member is being cared for with competence and is being kept comfortable.¹⁸⁷ Relatives also describe the importance of support from family and friends, an optimistic attitude and religious activities as other strategies for maintaining hope.¹⁸⁸ It is also important to receive information about what to anticipate in the situation and to be able to maintain family functioning during a time of crisis.¹⁸⁷ Hope gives energy that may help the family to cope and to expect that personal actions will be successful.^{189, 190} For families to achieve hopefulness and to avoid hopelessness in a critical situation, appropriate diagnoses and interventions may be valuable.¹⁸⁹ When an individual is unable to cope and perceives lack of control the predisposition for hopelessness increases, as do feelings of discouragement and that there is no use and sense.^{187, 189}

The team in the ICU need to assess the needs of families of critically ill persons to maintain hope.¹⁸⁹ They need to formulate routines early on in their meetings with relatives, to inform and allow relatives to make an early visit to the ICU after their significant other's admission.¹⁸² The situation of being a relative is distressing, and relatives coping strategies are mainly focused on different ways of achieving emotional relief for themselves.¹⁹¹ Relatives' coping strategies change over time. When the patient has been discharged from the ICU and hospital, relative's strategies are mainly focused on helping their significant other. Their own strength is being stretched to the limits because they need to cope not only with their own needs, but also with those of the patient.¹⁹¹

Relatives' experiences of a cardiac arrest survivor

Being a relative of a CA survivor is a unique experience not just because the event was unexpected, but also because of the heart disease and the uncertain neurological impact and outcome.^{24, 26, 152, 184} It is also a unique experience in that some relatives have been involved in their significant other's pre-hospital acute care and thus have been responsible for keeping him/her alive.¹⁸³ Being the relative of a CA survivor has been described as an unexpected chaotic situation that involves strong feelings.¹⁵²

The experience of initiating CPR is perceived as frightening and chaotic but relatives also describe their actions as rational.^{183, 184} Relatives also report feelings of guilt and are worry about not having performed CPR correctly, thus possibly causing their significant other's to suffer brain damage.^{183, 184}

During TH, the patient feels cold and looks pale, which relatives experience as unpleasant and extremely trying.^{152, 184} Any sign indicating that the situation could change causes strong emotions, and concerns about the future predominate.¹⁸³ Relatives are concerned and worried when their significant other wakes up, seems like a stranger and is unable to recognize them. Relatives are then concerned about whether this condition will be permanent.^{183, 184} Relatives are not always prepared for the challenges they will have to face following their significant other's discharge.¹⁸³

Rationale for the thesis

The purpose of resuscitation and subsequent hypothermia treatment is to regain patients' pre-CA status. During and after ROSC, post-CA cerebral blood flow is impaired and this is one factor that can cause neurological injury affecting outcome post-CA.^{107, 108} Measuring cerebral oxygen during post-resuscitation care and performing MRI on the brain are two methods that might be useful complements when clinicians predict prognosis and outcome in CA survivors. Even though survival is still low among CA patients an increase in survival has been noted. It is therefore valuable to evaluate prognostic tool that are in use, measuring survival and report neurological outcome in CA survivors, as well as increase knowledge of their relatives' experiences of the event. The above topics are addressed in the present thesis.

My interest in this area of research developed during my clinical practice as a critical care nurse in the ICU, a high technology environment associated with organ-specific care. My interest in CA-survivors' neurological outcome increased when TH became a part of the ICU care post-CA. The main questions in this thesis were: Is it possible to predict neurological outcome during ICU by measuring cerebral oxygen saturation? Can MRI, performed between 96-108 hours post-CA predict neurological outcome? What is the CA survivors' neurological outcome and what are the relatives' experiences 6 months after the event?

With increased knowledge in these areas the medical and nursing care may improve during ICU care and until discharge from hospital for both CA survivors and relatives. At the time of planning the study, there were sparsely of studies on CA-patients treated with TH and on physical and neurocognitive functioning 6 months after the arrest. Although there is knowledge about relatives of critically ill persons, no studies could be found on relatives' experiences and needs when a significant other was treated with TH post-CA.

Aims

The overall aim of the thesis was to investigate post-CA patients treated with TH with regard to prognostic tools, neurological and functional outcome up to 6 months after CA and their relatives' experiences in everyday life 6 months after the event. The specific aims of Papers I-IV were:

- I To describe variations in $SjvO_2$, differences in oxygen content between central venous oxygen saturation ($ScvO_2$) and $SjvO_2$, and oxygen extraction fraction from the brain (OEF_b) during intensive care in relation to neurological outcome at 6 months post-CA when target temperature management 33°C was applied.
- II To document the MRI findings in post-CA patients treated with TH and their relation to patients' neurological outcome.
- III To describe differences over time in functional outcome using CPC at discharge from the ICU and at 1 and 6 months after CA in cases where TH was used in post-resuscitation care. Additional aims were to describe differences in ADL and cognitive function in CA patients between 1 and 6 months after CA, life satisfaction 6 months post-CA and possible gender differences.
- IV To describe relatives' need for support and information, as well as the impact on everyday life, 6 months after a significant others' CA treated with TH.

Materials and methods

The present thesis consists of four studies, in which both quantitative (Papers I-III) and qualitative (Paper IV) methods were used (Table 2).

Table 2. *Overview of study design, population, data collection and analysis.*

Paper	Design	Study population	Data collection	Data analysis
I	Single-centre, prospective observational study	Two study groups of CA patients treated with TTM 33°C 2004-2007 & 2008-2012 (n=76)	Blood samples	Descriptive and analytic statistics
II	Multi-centre, prospective observational study	CA patients treated with TH 2008-2012 (n=57)	MRI	Descriptive and analytic statistics
III	Multi-centre, prospective observational study	CA patients treated with TH and who survived until 6 months. 2008-2012 (n=45)	Questionnaires: MMSE and BI at 1 and 6 months post-CA LiSat-11, 6 months post-CA	Descriptive and analytic statistics
IV	Multi-centre, descriptive with a qualitative approach	Relatives of CA patients treated with TH who survived. 2008-2010 (n=20)	Interviews 6 months after the event	Qualitative content analysis

BI= Barthel Index; CA= cardiac arrest; LiSat-11= Life Satisfaction-11; MRI= Magnetic resonance imaging; MMSE= Mini Mental State Examination; TH= Therapeutic Hypothermia; TTM 33°C= Target Temperature Management 33°C.

In all four studies, the same treatment protocol was used during the ICU care and regarding inclusion/exclusion criteria and TH. The study protocol was extended with a continuous aEEG during TH and MRI at 96-108 hours post-CA during the study period 2008-2012. Figure 2 provides an overview of the periods in which post-CA data were collected and investigated.

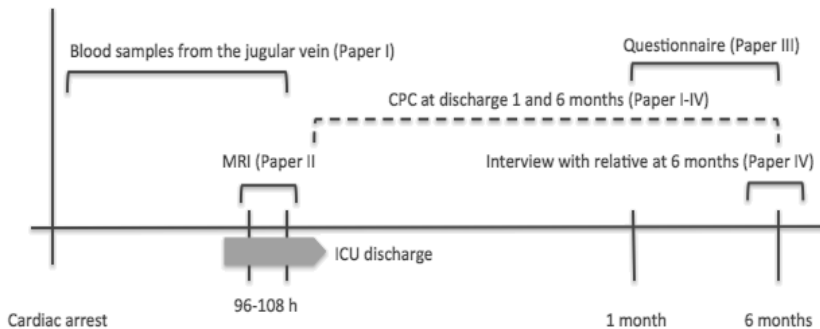


Figure 2. An overview of the periods in which post-CA data were collected and investigated.

Paper I

This was a prospective observational study and was conducted without any interventions related to the study variable cerebral oxygen saturation. The study included two cohorts of post-CA patients at the ICU and designed to investigate cerebral saturation in patients treated with target temperature management (TTM) 33°C.

Settings and participants

The study was performed in the 8-10 bed General ICU at Uppsala University Hospital and comprised CA patients treated with TTM 33°C, from two data collections between 2004-2007 and 2008-2012. The patients were eligible for inclusion if they were:

- Comatose with a Glasgow Coma Scale (GCS)¹³⁸ < 8 or a Reaction Level Scale (RLS 85)¹⁹² >3 after successful ROSC
- Systolic arterial blood pressure \geq 80 mmHg > 5 minutes,
- Regardless of first registered ECG rhythm or whether the CA occurred in or out of hospital

If these criteria were fulfilled decisions for TTM 33° were taken and a jugular bulb catheter inserted. Patients were excluded with:

- Suspected pregnancy
- Terminal illness and/or pre-existing coagulopathic disease
- Age <18 years

During the study period, 240 CA patients were admitted to the ICU, 190 were treated with TTM 33°C and of these 80 were not eligible for inclusion, i.e. 110 were treated with TTM 33°C. Seventy-six patients received a jugular bulb catheter and were included in the study (Figure 3).

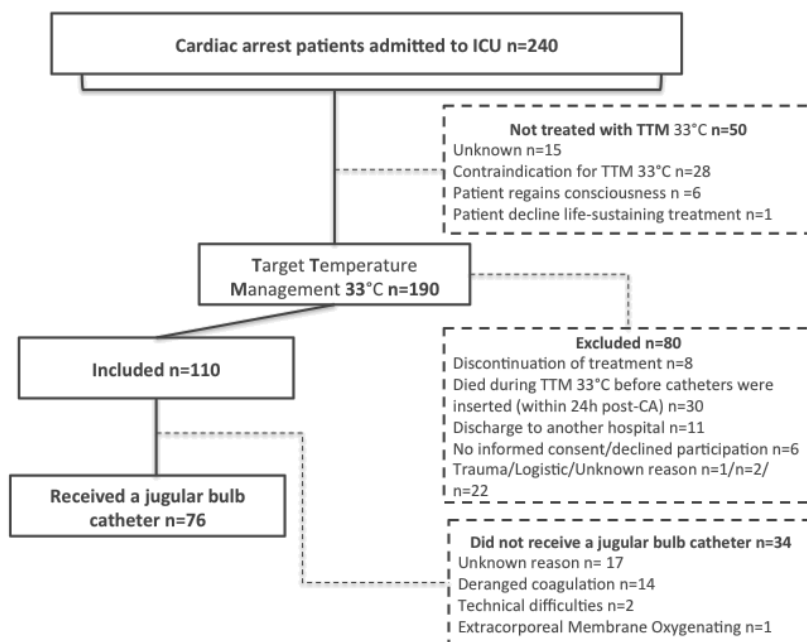


Figure 3. Flow chart over CA patients admitted to ICU.

Treatment protocol

Hypothermia was induced at the emergency department or when the patient was admitted to the ICU. Hypothermia treatment was induced by cold 4°C intravenous saline infusion in a planned volume of 30-40 ml/kg using positive pressure infusion into two peripheral intravenous catheters. Simultaneously, ice packs were applied to the groins, axillae and along the carotid arteries and were changed when necessary to enable continuous cooling. Before TTM 33°C was introduced all patients were sedated, intubated and ventilated according to guidelines for seriously ill patients adapted for TTM 33°C post-CA.⁶⁸ Patients were sedated with a propofol infusion given at a dose of 0.3-4mg/kg/h, and a fentanyl infusion at 1-3ug/kg/h. In the event of shivering the patient first received additional sedation and analgesia. If this

was not sufficient a muscle relaxant (rocuronium) was added as a bolus injection of 0.6 mg/kg and if required as an infusion at 0.15mg/kg/h. Ventilation was set to maintain a PaO₂ ≥12 kPa (>90 mmHg) and PaCO₂ of 5.0-5.5 kPa (38-41 mmHg). The target for blood pressure was defined as a mean arterial pressure (MAP) ≥60 mmHg, and if required, volume infusion, vasoactive (norepinephrine) or inotropic (dobutamine) medication was administered. The planned duration of TTM 33°C was 24 hours. In line with the ICU routines patients were cared with a 30° elevation of the head.

The planned duration of TTM 33°C was 24 hours. It was estimated that the first two hours post-CA would be taken up by transportation to hospital and decisions about TTM 33°C. The target temperature of 32-34°C was therefore maintained for up to 26 hours after the estimated time of CA. Passive rewarming at 0.5°C/hour started after 26 hours. It was expected that a temperature of 36°C, which was considered the normal core temperature would be reached within 8 hours. Core temperature was measured continuously in the urinary bladder (Curity silicon thermistor 400 series catheter, Tyco Healthcare, United Kingdom).

In addition to an arterial line in the radial or femoral artery and a central venous catheter within 24 hours post-CA patients also received a single lumen catheter 7Fr, which was introduced into the right jugular vein and directed cranially with its tip in the right jugular bulb. In all patients a lateral neck radiographic verification of correct placement of catheters was obtained i.e. above the disc space between C1 and C2. Every 90-120 minutes, blood samples were drawn for measurement and analysis of blood gases, (ABL 700, Radiometer Triolab AB, Copenhagen, Denmark). Neurological outcome was assessed using the CPC scale¹³⁸ (Table 1).

Neurological outcome was assessed when patients had achieved normal core temperature, and assessment was repeated daily at the ICU, at discharge from ICU and at 6 months post-CA. The CPC assessment was conducted by reading the medical journal, by a phone call or in a personal meeting with the patient. A neurologist performed repeated clinical examinations, in addition to SSEP. In the first study period, intermittent EEG was performed when clinical suspicion of seizures occurred. In the second study period, a continuous aEEG and MRI were performed as a routine. The analyses from these investigations are not presented in this study.

Withdrawal of care

Intensive care post-CA followed the same priorities and ethical considerations as other intensive care, i.e. patients were prioritized based on the function of and prognosis for all vital organs, which determined whether active treatment was required or should be continued.^{77, 82, 83} Neurological prognostication and withdrawal of care followed the recommendation from the Swe-

dish Resuscitation Council and was determined by the attending physician.⁸³ The analyses and the results from the jugular venous blood were only followed and documented; they were not used in the treatment, for prognostication or for withdrawal of care.

Data collection and procedure

Samples of blood from the arterial line, jugular bulb catheter, and central venous catheter were taken simultaneously as soon as the catheters were in place and again 6, 12, 18, 24, 36, 48, 60, 72, 84, 96 and 108 hours post-CA or as long as the patients were at the ICU. Divergence of ± 2 hours in the sampling schedule was accepted. Blood samplings that diverged by more than 30 minutes between sampling from the arterial line, jugular bulb catheter and central venous catheter were excluded from the analysis. This was done to avoid changes in treatment that might have affected the analysis. Owing to missing data, there was some variation in number of samples between the seven time points. Reasons for this were that the jugular bulb catheter had not been inserted, mainly during 6 and 12 hours post-CA. Furthermore, the number of patients decreased across the time points due to death or ICU discharge before 108 hours.

Demographic and medical data related to the CA were collected from medical charts.

Statistical analysis

Analyses for arterial oxygen saturation (SaO_2), SjvO_2 and central venous oxygen saturation (ScvO_2) were conducted between selected time points in the hypothermic phase (at 6, 12 and 24 hours) and when patients were expected to have achieved normal core temperature (48, 72, 96 and 108 hours) post-CA. The difference in oxygen between central venous blood and jugular venous blood was expressed by $\text{ScvO}_2 - \text{SjvO}_2$ and OEF_b was calculated as $(1 - \text{SjvO}_2 / \text{SaO}_2) \times 100$. Data from the measurements are expressed as median and interquartile ranges (IQR). The data were dichotomized into good (CPC 1-2) and poor (CPC 3-5) neurological outcome. Chi-squared test or Fisher's Exact test was used to compare demographic and medical data. Because the data were not normally distributed, Mann Whitney U-test was used when comparing saturation between patients with good and poor outcome. Demographic and medical data are presented using descriptive statistics and expressed as median, IQR or absolute numbers and percentages. A p-value < 0.05 (two-tailed) was considered to be statistically significant. The statistical analyses were performed using SPSS version 21 (SPSS Inc. Chicago, IL, USA).

Paper II

This study was a prospective observational study performed at three ICU departments; it investigated MRI findings on post-CA patients treated with TH.

Settings and participants

The study was conducted in three hospitals, one university hospital and two general county hospitals, during 2008-2012. Inclusion, exclusion and treatment followed the same priorities, as for Paper I. MRI of the brain was obtained at all three hospitals in all CA survivors if no contraindications existed.

MRI was performed in 57 patients, regardless of level of consciousness post-CA. The intended timing of MRI was between 96-108 hours post-CA. Reasons for exclusion and the outcome data are presented in Figure 4. A cardiologist evaluated patients and those eligible for invasive procedures were transported to the catheterization laboratory for procedures. At the university hospital, SSEP was obtained between 96-108 hours post-CA and simplified amplitude-integrated EEG monitoring was carried out continuously during TH and until patients had reached normal core temperature. Neurological prognostication and withdrawal of care followed the recommendation from the Swedish Resuscitation Council and was determined by the attending physician⁸³ and followed the same principles as for Paper 1.

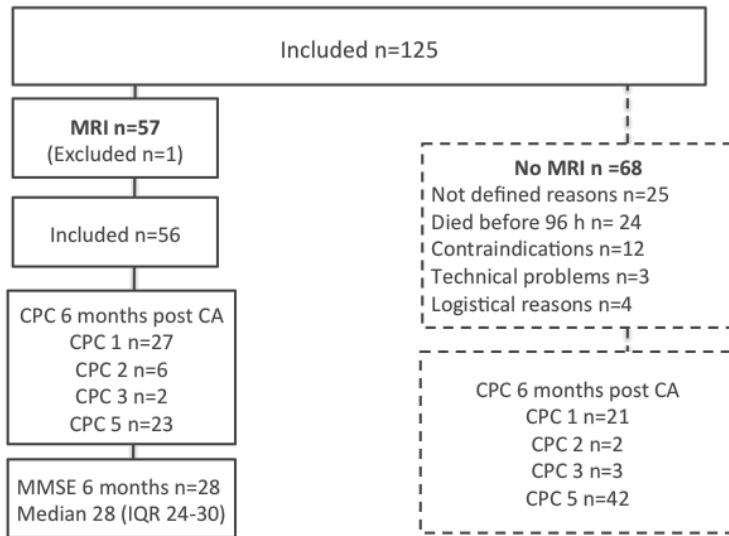


Figure 4. Flow chart of cardiac arrest patients admitted to intensive care unit (ICU) and where magnetic resonance imaging (MRI) was performed. CPC; Cerebral Performance Categories, ICU; intensive care unit, MMSE; Mini Mental State Examination, TH; Therapeutic Hypothermia.

Data collection and procedure

Neurological outcome

Neurological examinations using RLS 85¹⁹² were performed at 48 and 108 hours post-CA in the ICU. The RLS 85 is an arranged scored coma scale (8 levels), where 1-3 means that the patient is conscious and 4-8 means that the patient is in coma.¹⁹² The RLS 85 score at 48 hours was used to estimate level of consciousness before MRI was performed. Neurological outcome was assessed using the CPC¹³⁸ at ICU discharge and 6 months post-CA (Table 1). Good functional outcome was defined as CPC 1-2 and poor outcome CPC 3-5. To evaluate the cognitive function in patients who scored good outcome at 6 months, the mini mental state examination test (MMSE) was used. The MMSE is a quantitative screening instrument intended to evaluate the patient's cognitive function.¹⁹³ It includes questions regarding orientation, memory, counting and the ability to follow written and oral instructions. The score range is 0–30.¹⁹³ Patients scoring below 24 are classified as having cognitive dysfunction.¹⁹³

MRI technique and analysis

Fifty-six examinations were performed with 1.5 T MR systems and one with a 3 T system. Brain images were obtained using a standard imaging protocol, including T1-weighted sagittal spin echo (SE) images, T2-weighted axial and coronal turbo SE images and T2-weighted axial fluid-attenuated inversion recovery (FLAIR) images. In 46 patients T2*-weighted axial gradient echo (GRE) images were obtained. DWI was performed using a SE echo planar imaging (EPI) sequence and b values of 0 and 1000. Two experienced neuroradiologists (EML and RR) carried out visual analysis of the images independently. Cases with a discrepant interpretation were discussed, and consensus on scoring was reached. Locations and sizes of acute ischemic lesions, i.e. those with decreased diffusion on apparent diffusion coefficient (ADC) maps, were recorded. The sizes of the lesions were classified according to the largest diameter (Table 3).

Table 3. *Classification of the lesion size according to the largest diameter*

Category	Ischemic lesions size, cm
1	<1.5 cm
2	1.6-5 cm
3	>5 cm

Bleedings and bleeding rests, atrophy, old infarcts and degenerative white matter changes, probably caused by a chronic small vessel disease, were recorded. Signs of small vessel disease were classified in categories and are illustrated in Table 4.

Table 4. *Classification of small vessel disease*

Category	Lesions size, mm
0	No or a few lesions, diameters ≤ 5 mm
1	Focal lesions with diameters > 5 mm
2	Confluent lesions

Besides a visual examination, ADC was measured in pre-specified areas in the foramen semiovale, frontal and occipital white matter, putamen, thalamus, pons, and cerebellum. The regions of interest (ROI) were manually drawn in the morphological images and coregistered in the diffusion images using the in-house software Eval Gui, developed by Markus Nilsson, Lund University, Lund, Sweden. The measurements were made using the same software. The first author (EW) drew the ROIs and the neuroradiologists controlled the placements. ROIs were placed to avoid lesions other than those with probable acute ischemic aetiology. The neuroradiologists were blind to neurological outcome.

Statistical analysis

Demographic and medical data are presented using descriptive statistics and expressed as median with interquartile ranges (IQR) or absolute numbers and percentages. The material was dichotomized into good (CPC 1-2) and poor (CPC 3-5) neurological outcome. Chi-squared test or Fisher's Exact test and Mann Whitney U-test were used to compare demographic and medical data. A p-value <0.05 was considered to be statistically significant. The results from visual image analysis are presented descriptively, and where suitable non-parametric tests were used to compare differences in neurological outcome. The statistical analyses were performed using SPSS version 21 (IBM, SPSS Inc. Chicago, IL, USA).

Paper III

Paper III was performed at three intensive care units in Sweden between May 2008 and May 2012 and focus was on survivors of CA. It was a quantitative study designed to investigate physical and cognitive function and life satisfaction in CA survivors treated with TH.

Settings and participants

Inclusion, exclusion and treatment followed the same priorities, as for Paper I. Furthermore, to be eligible for inclusion in this follow-up study, patients were able to speak and understand the Swedish language, understand and answer the questions used in the study and answer all questionnaires at both occasions.

A total number of 125 CA patients were treated with hypothermia after CA, 63 survived until discharge from hospital. A total number of 62 patients died before hospital discharge; the causes of death were hypoxic brain injury in 60%, cardiac cause in 27%, and respiratory failure in 6.5% and multi-organ failure in 6.5%.

Eighteen patients were excluded from the follow-up study because they were not able to answer the questionnaires at both occasions, remaining 45 patients eligible for the follow-up study. Reasons for exclusion were severe disability or death during the follow-up study in nine patients, languages/logistical difficulties in eight patients and one patient declined participation.

Data collection and procedure

Socio-demographic variables prior to the CA were collected by self-report or by relatives and main medical variables related to the CA were collected

from medical charts. At 6 months, information on work situation and healthcare visits was collected through self-report. The functional outcome measurements were CPC¹³⁸ (Table 1), Barthel Index (BI),¹⁹⁴ MMSE)¹⁹³ and life satisfaction (LiSat-11).¹⁹⁵

Measurements with CPC were made at discharge from ICU, 1 and 6 months after CA.

Barthel Index

The BI was used as self-report instrument and produces a simple index of independence in ADL. The instrument is useful in scoring improvement in rehabilitation.¹⁹⁴ The BI consists of 10 variables measuring three categories of function; self-care, continence of bowel and bladder and mobility. The total score is from 0-100.¹⁹⁴ A high score is associated with greater likelihood of being independent and living at home at discharge from hospital.^{194, 196}

Mini mental state examination

The MMSE is a quantitative screening instrument intended to evaluate the patient's cognitive function. The first section includes orientation, memory, counting and attention and requires a verbal response. The second section addresses the ability to follow written and oral instructions, type a phrase spontaneously and copy a figure. The score range is 0-30.¹⁹³ A cutoff score below 24 was used to demonstrate cognitive dysfunction.¹⁹³ The BI and MMSE were assessed at 1 and 6 months.

Lisat-11

The LiSat-11 was used as a self-report instrument at 6 months after CA and encompasses eleven domains assessing overall and domain-specific life satisfaction.¹⁹⁵ The first domain characterizes satisfaction "with life as a whole". The remaining ten domains characterize vocational, financial, and leisure situations, social contacts, sexual and family life, self-care, partnership and somatic and psychological health. The LiSat-11 uses a six-step ordinal self-rating scale ranging from 6= very satisfying to 1= very dissatisfying.¹⁹⁵ LiSat-11 scores were dichotomized into satisfying to very satisfying (5-6) and rather satisfying to very dissatisfying (1-4), which is considered a valid scale reduction.¹⁹⁵

Statistical analysis

Descriptive statistics and results are presented as frequencies, percentages and as means with standard deviations. Statistical analyses were performed using SPSS version 21 (SPSS Inc. Chicago, IL, USA). Due to the small sample size, the Wilcoxon signed rank test and Friedman's test were used to

describe differences over time. The Mann Whitney U-test and the chi-squared test were used to analyse differences between included and excluded patients as well as between genders. Given the multiple tests performed, a p-value ≤ 0.01 was considered statistically significant. The reliability of the instruments was expressed as Cronbach's α coefficient.

Paper IV

The design was descriptive and had a qualitative approach. The participants were interviewed six months after their significant other's CA.

Settings and participants

The participants (n = 20) had a relative who had survived a CA treated with TH in the ICU at the university hospital or one and two general county hospitals in Sweden from May 2008 to June 2010. A relative was defined as someone close whom the patient trusted. To obtain as much variation as possible, participant selection was done purposefully with regard to age, sex and relationship¹⁹⁷ (Table 5). In this study relatives participating in the study are referred as "relatives" and patients who survived CA will be referred to as "significant other".

Table 5. *Demographic data for relatives.*

Sex	Age	Relation to the patient	Working situation at the time of the CA	Working situation at 6 months
14 Women	20-70 years	13 partners	13 worked full time	10 worked full time
6 Men	(Mean =55)	6 children 1 parent	3 worked part time 1 student 3 retired or sick listed	5 worked part time 1 Study break 4 retired or sick listed

Data collection

The interviews were semi-structured. An interview guide with topic areas to be covered was used. The introductory question was "Describe how your life has been affected during these months after your significant other's cardiac arrest". The remaining topic areas included what support the relative had received, the need for additional support and thoughts about the future. The second author, the last author and one collaborator, all of whom are ICU nurses and were involved in the study, performed the interviews. The relative chose the place and time for the interview, which was typically the rela-

tive's home. Four interviews were conducted over the phone because of the geographic distances involved.

Data analysis

The intention was to describe relatives' experiences of everyday life six months after a significant other had a CA treated with TH. Therefore the interviews were analysed using qualitative content analysis.¹⁹⁷⁻¹⁹⁹ Qualitative description is a method used for classification of experiences and to answer questions such as "who, what and where".^{198, 200} The method is defined as analysing a text in a systematic way.²⁰¹ Qualitative content analysis is conducted by considering the descriptive (manifest) content and is described in categories or subcategories. The underlying meanings (latent content) are used to create themes.¹⁹⁹ In this study, the latent content was used. The process of analysing the interviews is a reflective one and involved back and forth movements between the whole text, the codes and the categories for each theme. An open dialogue was maintained with the authors continuously during the analysis process to reach a consensus on the findings. The process of analysing is described below:

1. The interviews were transcribed verbatim.
2. The first author listened to the audiotapes and read through the transcribed text several times to gain a sense of the content as a whole.
3. Each interview was analysed separately.
4. The text was divided into meaning units in line with the aim. A meaning unit could consist of words, sentences or paragraphs.
5. The meaning units were condensed (shortening the text without losing the core signification) and were then abstracted and sorted into codes.
6. The codes were compared based on similarities and differences and sorted into categories based on similarities.
7. Categories with similar content and underlying meaning were sorted into the same themes. The authors went back and forth between the interviews, codes, categories and themes to validate the findings throughout the analysis process.

Ethical considerations

The studies were performed according to rules laid down by the Declaration of Helsinki²⁰² and reviewed and approved by The Regional Ethical Committee in Uppsala (reg. no 2004:M-207 and 2007/307). All participants received verbal and written information regarding the purpose of the study. The patients who participated in these studies were at no risk, voluntariness was emphasized and confidentiality was guaranteed. In all studies a relative was

informed about the study and asked to give informed consent on the patient's behalf and later consent was obtained from survivors.

Patients in Paper III were asked to participate in the follow-up study about a week after ICU discharge or before discharge from the medical ward. There could be a risk of feeling pressured to participate for patients, as they were still at hospital when they were asked to participate. This was judged to be minor, because the nurse who gave information and obtained informed consent was not involved in the care at the medical ward. In Paper IV, CA survivors were asked when health permitted, most often about a week after ICU discharge, whether they would allow a relative to be interviewed regarding how his/her everyday life has been affected six months after the event. A relative was defined as someone close whom the patient trusted.

As a researcher you need to be respectful towards both patients and their relatives and clarify that the decision to participate or not will not influence the care given. Furthermore you need to be aware that CA survivors may have cognitive impairments post-CA that influence their memory and therefore they may not remember that they previously gave their consent. Therefore information about the study was repeated during the follow-up period.

Results

Paper I

Seventy-six patients received a jugular bulb catheter during the study period. One patient was excluded from the analyses due to missing values at all time points, leaving data from 75 patients.

Thirty-seven (47%) of the included patients survived with a good outcome (CPC 1-2) at 6 months. The baseline characteristics of the included patients are provided in Table 6.

Table 6. *Demographic and medical characteristics.*

	All patients n=75	Good outcome n=37	Poor outcome n=38	P-value
Age ^a	68 (57-78)	61 (53-70)	73(67-79)	<i>p</i> =0.001
Gender^b				
Male	51 (68)	30 (81)	21 (55)	<i>p</i> =0.025
Female	24 (32)	7 (19)	17 (45)	
Initial ECG rhythm^b				<i>p</i> =0.004
VF/VT	37 (49)	25 (68)	12 (32)	
Asystole/PEA	34 (46)	11(30)	23 (60)	
Unknown	4 (5)	1 (2)	3 (8)	
OHCA ^b	56 (75)	30 (81)	26 (68)	ns
Witnessed CA ^b	64 (85)	31 (84)	33 (87)	ns
Minutes from CA to TTM 33°C ^a	300 (194-503)	390 (217-562)	270 (153-398)	<i>p</i> =0.000
Minutes from start of rewarm- ing to 36°C ^a	600 (465-814)	585 (435-795)	600 (480-820)	<i>p</i> =0.002
ICI stay in days ^a	4 (3-79)	5 (3-9)	4 (3-6)	ns
Coronary angiography ^b	36 (48)	23 (62)	13 (34)	<i>p</i> =0.021
PCI ^b	19 (25)	13 (35)	6 (16)	ns
Medical history^b				
No previous illness	18 (24)	13 (36)	5 (13)	ns
Ischemic heart disease	21 (28)	10 (27)	11 (29)	ns
Heart failure	22 (29)	9 (24)	13 (34)	ns
Hypertension	28 (37)	14 (38)	14 (37)	ns
Lung disease	9 (12)	2 (5)	7 (18)	ns
Diabetes	15 (20)	6 (16)	9 (24)	ns
Stroke	8 (11)	1 (3)	7 (18)	ns
Malignancy	5 (7)	1 (3)	4 (11)	ns

CPC ICU^b				p=0.000
CPC 1	4 (5)	4 (11)	0	
CPC 2	22 (29)	22 (60)	0	
CPC 3	15 (20)	10 (27)	5 (13)	
CPC 4	8 (11)	1 (3)	7 (18)	
CPC 5	26 (35)	0	26 (68)	
CPC at 6months^b				
CPC 1	31(41)	31 (84)	0	
CPC 2	6 (8)	6 (16)	0	
CPC 3	2 (3)	0	2 (5)	
CPC 5	36 (48)	0	36 (95)	

CA=cardiac arrest, VF=ventricular fibrillation, VT=ventricular tachycardia, PEA=pulseless electric activity, ROSC=return of spontaneous circulation, ICU=intensive care unit, OHCA=out-of-hospital-cardiac arrest, PCI=percutan coronary intervention, CPC=cerebral performance category, ns= not significant. Categorical data presented as number of total, *n* (%) and compared using chi-square test. Continuous data presented as median and interquartile (IQ) and compared using Mann-Whitney U test.

^aMedian (IQR)

^bNumber of patients (%)

Among patients with poor outcome status epilepticus was verified in four (5%) patients; seizures were documented in two additional (3%) of patients, but not verified as status epilepticus. A pathologic pattern without seizures was documented in 16 (21%) patients, and in the remaining 53 (71%) patients, no seizures or pathologic patterns were recognized.

The main reasons for withdrawal of care post-CA in the present study within 72-108 hours post-CA was due neurological damage (n=28). In one patient brain infarct was diagnosed within 72 hours. In seven patients treatment was withdrawn within 24-72 hours due to non-responsive cardiogenic shock. In two patients further ICU care was restricted and readmission to ICU limited.

Jugular bulb oxygen saturation

Patients with poor outcome showed higher values for S_{ijv}O₂ at 6, 12, 96 and 108 hours, and was significant at 12, 96 and 108 hours (Figure 5). An S_{ijv}O₂ value <55% of the potential ischemic threshold was seen in 23 (43%) patients at the measurement made 6 hours post-CA. Twelve (52%) patients with S_{ijv}O₂ values <55% at 6 hours survived with a good outcome. S_{ijv}O₂ increased across the measurement occasions, and at 108 hours there was one patient with an S_{ijv}O₂ value <55%. An S_{ijv}O₂ > 75% was seen in at all time points, and no differences were seen between patients with good and poor outcome.

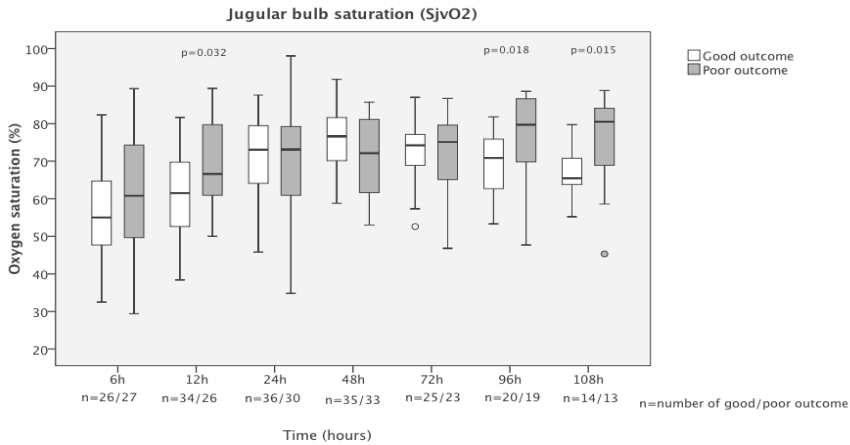


Figure 5. The venous jugular bulb oxygen saturation (SjvO₂) in patients with good vs. poor outcome during TTM 33°C and normal core temperature. Line= median; the outer limits of the box = interquartile, the whisker = non-outlier range the outliers are indicated with an ○. White represents good outcome and grey poor outcome. Patients with poor outcome had higher values, but this was only significant at 108h in 26 post-CA patients.

Differences in oxygen content between ScvO₂ and SjvO₂

The median values in ScvO₂-SjvO₂ were higher in patients with good outcome at 6 hours ($p=0.01$) but not at the other measurement points (Figure 6).

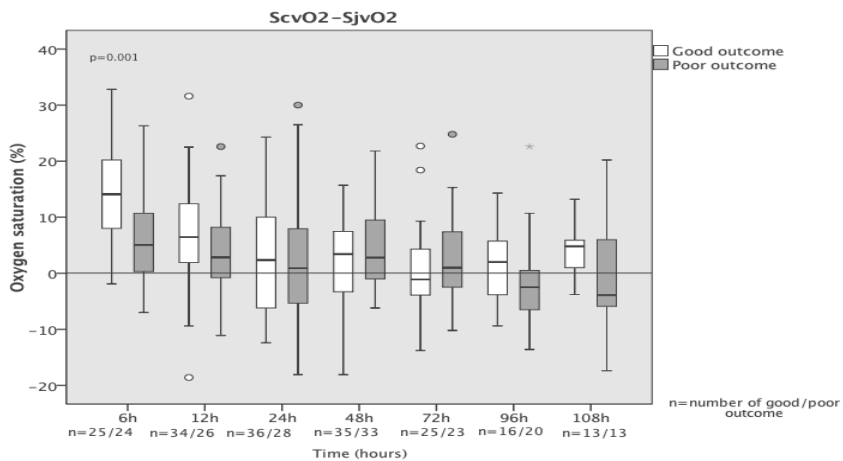


Figure 6. Illustrating the difference between central venous oxygen saturation (ScvO₂) and jugular bulb oxygen saturation (SjvO₂) in patients with good vs. poor outcome during TTM 33°C and normal core temperature. Line= median; the outer limits of the box = interquartile, the whisker = non-outlier range the outliers are indicated with an ○. White represents good outcome and grey poor outcome

Oxygen extraction fraction of the brain

Differences in OEF_b values were seen at 6, 12, 96 and 108 hours, where patients with poor outcome had lower values (Figure 7). OEF_b decreased to <25% during the period 24 hours to 96 hours post-CA in patients irrespective of outcome.

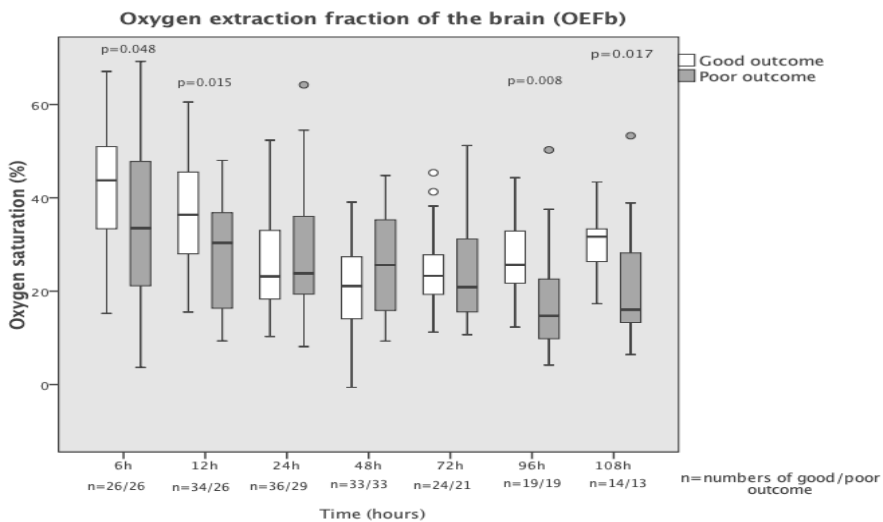


Figure 7. Box plot illustrating the oxygen extraction fraction (OEF_b) between central venous oxygen in patients with good vs. poor outcome during TTM 33°C and normal core temperature. Line= median; the outer limits of the box = interquartile, the whisker = non-outlier range the outliers are indicated with an ○. White represents good outcome and grey poor outcome.

Paper II

DW images and ADC maps were of poor quality in one patient. Therefore we present the results for 56 patients.

Asystole was more common ($p=0.04$) in the group with poor outcome. Patients who survived with a good outcome were younger ($p=0.006$) and spent more days in hospital ($p<0.001$) compared to patients with a poor outcome. Demographic data, time for MRI and neurological outcome are illustrated in Table 7.

Neurologic outcome

In seven patients, prior to MRI, RLS scoring was missing at 48 hours. Eight patients did not regain consciousness before the MRI, but survived with good outcome. The MMSE was performed in 28/33 (85%) patients, and the median MMSE was 28 (IQR 24-30). Seven out of 28 patients were scored as cognitively impaired i.e. MMSE <24. The MMSE was not performed in five patients with good outcome for logistical reasons and/or owing to inability to speak and understand Swedish (Table 7).

Table 7. Demographic data, time for MRI, CPC and MMSE in patients post-CA.

Sex	Age	MRI	RLS \leq 3 48 hours n, (%)	Good outcome n, (%)	MMSE
36 Male	23-82 years (Median=65)	3-13 days (Median 4 days)	25 (51%)	32 (57%)	12-30 (Median 28)

Values are presented as min-max. CA= cardiac arrest, CPC= cerebral performance category, MMSE= mini mental state examination, MRI= magnetic resonance imaging.

Visual image analysis

Lesions with decreased diffusion, which was regarded as a sign of cytotoxic oedema, were interpreted as acute hypoxic/ischemic lesions. They were found in 34 (61%) patients and were more common in patients with poor outcome (χ^2 (df=1)=7.8, $p=0.006$) (Figure 8).

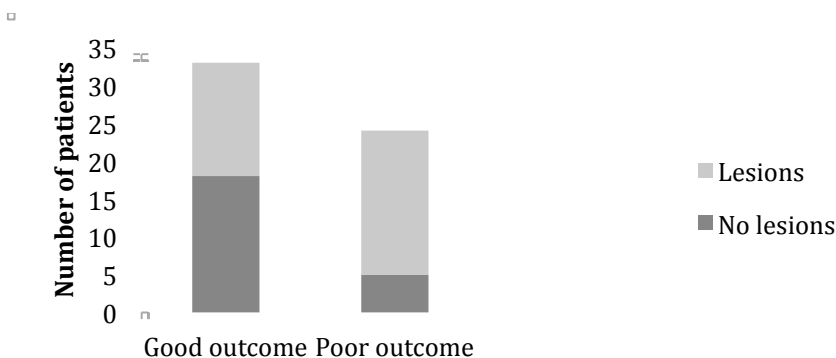


Figure 8. Number of patients with acute hypoxic/ischemic lesions on MRI

Representative examples of patients with different radiological lesions and varying outcomes are presented in Figure 9-11.

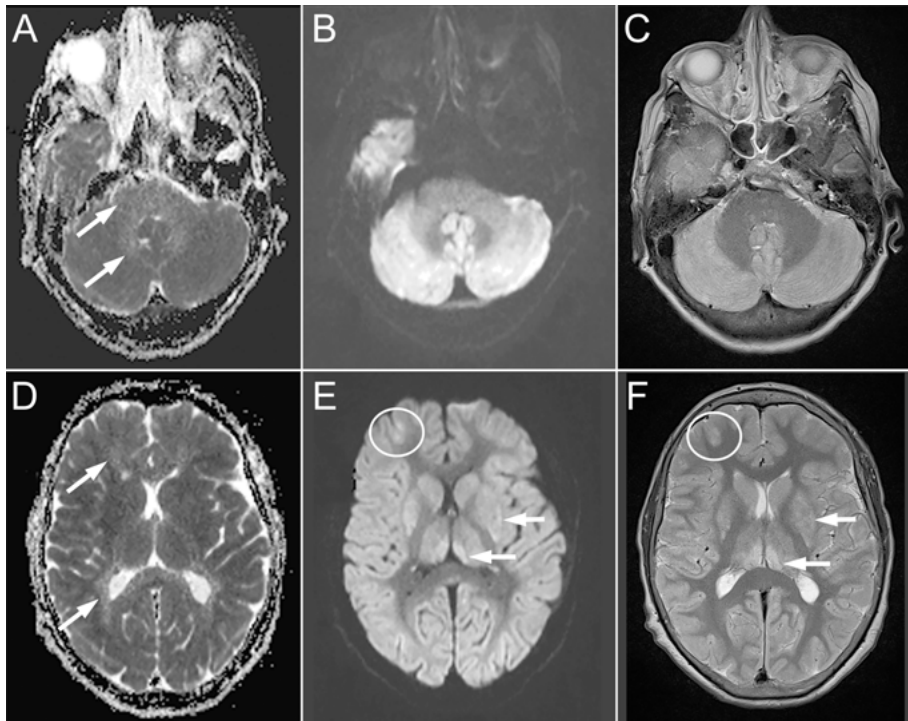


Figure 9. MRI 61 hours after cardiac arrest in a 78-year-old woman with 35 min to ROSC (asystole), died 6 days after cardiac arrest. MRI demonstrates very large acute hypoxic/ischemic lesions both in the cerebellum, (upper row) and cerebrum (lower row). ADC maps (A, D) show that most of the brain areas are dark because of restricted diffusion. Regions with normal diffusion (brain stem, regions of the dentate nuclei and around the arteria of the lateral ventricles, internal capsules and small areas anterior to the frontal horns) are marked with arrows. Entire cortex in the cerebellar and cerebral slices and the deep gray matter are abnormally bright in diffuse-weighted images (DWI) (B, E). The same areas are hyperintensive in T2-weighted SE images (C, F). The most hyperintensive areas (ring and arrows) in the T2-weighted areas are extremely hyperintensive also in DWI because DWI also are affected by relaxation time. See Fig.1 to compare with normal appearance of the brain.

Few or none acute lesions in MRI are illustrated in figure 10 in a patient surviving with poor outcome in figure 11 in a patient surviving with good outcome.

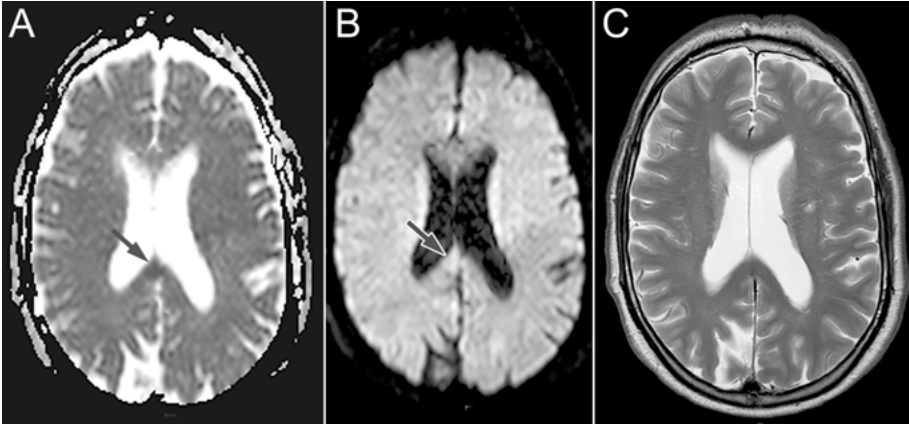


Figure 10. MRI 59 hours after cardiac arrest in a 70-year-old man with 30 min to ROSC (asystole), survived with a poor outcome i.e., CPC 3. MRI shows an acute lesion in the corpus callosum (arrow). Restricted diffusion is seen as a dark area in the ADC map (A). Signal intensity is high on DWI (B). Nothing pathological can be seen in the T2 weighted image (C).

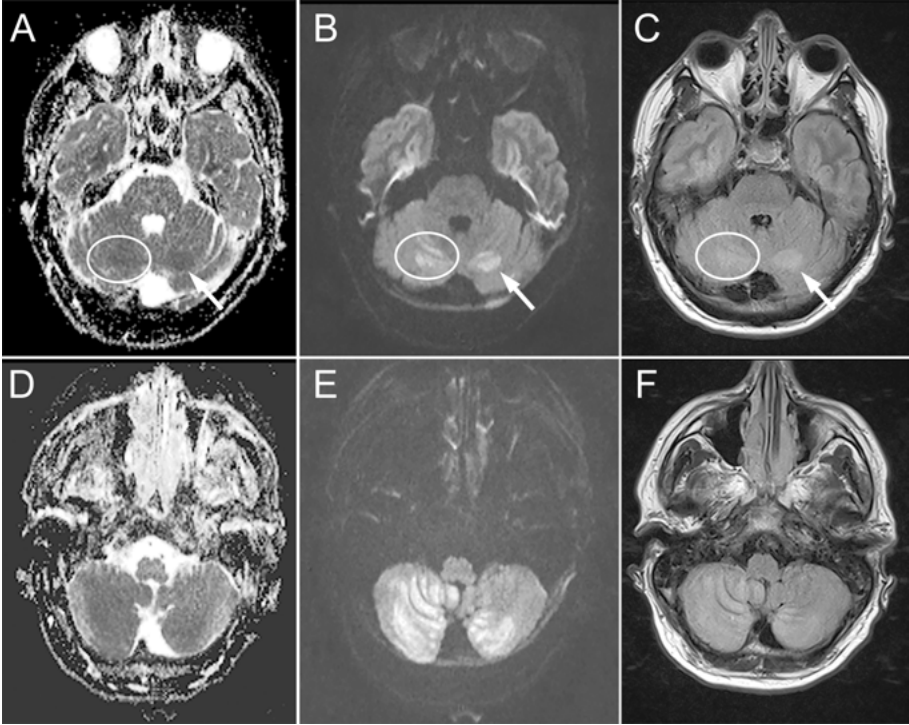


Figure 11. MRI 89 hours after cardiac arrest in a 42-year-old man with 90 min to ROSC (VF), surviving with good outcome and scoring 27 on the MMSE. MRI shows acute hypoxic/ischemic lesions in the cerebellum. The lesions are smaller in the lower slice (upper row, ring and arrow) but in the slice of a higher level (lower row) most of the right hemisphere is pathological and there is a large lesion also in the left hemisphere). The affected area is dark in the ADC maps (A, D) but hyperintense in the DWI (B, E) and in the T2-weighted images (C, F).

The changes in DWI involved mainly the cerebral cortex, deep gray matter and cerebellum (Figure 12). An increased number of lesions were associated with a poor outcome. Lesions in the occipital and temporal lobes, deep gray matter (i.e. the basal ganglia and thalami) and the cerebellum were most associated with poor outcome.

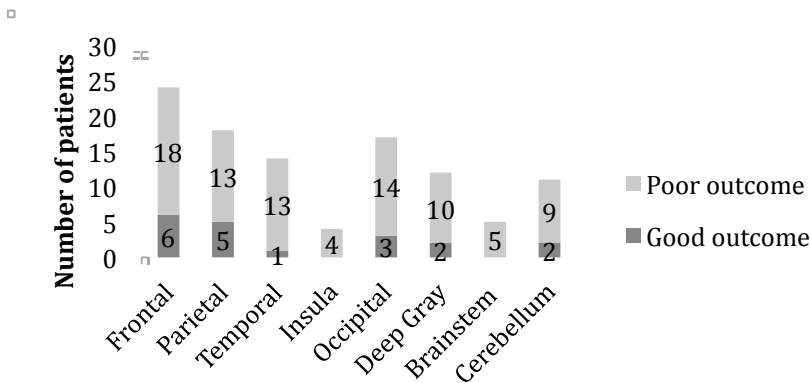


Figure 12. Relation of lesions located in certain brain regions and outcome. Significant differences were seen between patients with good and poor outcome in all brain regions with a variation of $p=0.007-0.000$, using Fishers' Exact test. Deep gray = basal ganglia and thalami.

Eleven patients had very large lesions i.e. category 3 (Table 3) and none of them survived. Three patients with motor cortex lesions survived with good outcome. Deep gray matter involvements, i.e. lesions in the thalami and basal ganglia, were observed in 12 patients and only two of them survived with good outcome. T2*-weighted images revealed minimal haemorrhages in acute lesions of six patients and 5 of them had poor outcome. Old infarcts, including all types of infarcts from lobular to lacunar, were found in 11/56 patients and seven of them survived with a good outcome. Thus presence of earlier infarcts did not affect outcome. T2 hyperintensities, characteristic of small vessel disease (Table 4), were identified in 32 patients (22 in Category 1, 10 in Category 2) but did not affect outcome (χ^2 (df=2)=2.8, $p=0.270$). Atrophy was observed in 22/56 patients and 13 of them survived with a good outcome; no differences were seen between good and poor outcome ($p=0.813$).

ADC measurements

ADC measurements were successfully made in 49 patients. In two patients, the ADC measurements in the cerebellum were excluded due to large, old post-infarct changes. No significant differences between patients with good outcome vs. poor outcome were detected except in the occipital lobes, where ADC values were significantly lower in patients with a poor outcome (right $p=0.004$, left $p=0.018$) (Table 8). No patients with ADC values below $600 \times 10^{-6} \text{mm}^2/\text{s}$ in any region survived. Patients with high ADC values, regarded as a sign of extracellular oedema could have good or poor outcome.

Table 8. *ADC measurements in pre-specified areas.*

Location	ADC values			P-value
	All patients (n=49)	Good outcome (n=28)	Poor outcome (n=21)	
Cerebellar white matter right	(n=47) 717 (690-751)	(n=26) 719 (696-759)	712 (664-743)	ns
Cerebellar white matter left	(n=48) 709 (672-751)	(n=27) 722 (687-759)	688 (715-809)	ns
Pons	(n=48) 767 (731-809)	(n=27) 762 (736-812)	773 (715-809)	ns
Thalamus right	790 (751-827)	787 (750-832)	790 (756-827)	ns
Thalamus left	780 (749-818)	781 (748-834)	768 (750-846)	ns
Putamen right	735 (689-780)	757 (698-799)	709 (675-774)	ns
Putamen left	734 (679-795)	749 (695-781)	703 (660-813)	ns
Occipital white matter right	838 (757-868)	846 (809-878)	757 (662-867)	$p=0.004$
Occipital white matter left	833 (753-871)	843 (810-879)	755 (638-862)	$p=0.018$
Frontal white matter right	794 (734-839)	775 (729-836)	800 (743-846)	ns
Frontal white matter left	777 (711-832)	762 (711-826)	798 (719-837)	ns
Centrum semiovale right	753 (702-815)	741 (698-811)	766 (708-817)	ns
Centrum semiovale left	763 (723-839)	747 (710-836)	772 (750-870)	ns

ADC; apparent diffusion coefficient, ns; non significant

Paper III

A total of 45 participants were included and answered the instruments at two occasions. Mean age was 64 years and 25 (63%) were males. At the time of CA, 10 (22%) were working fulltime and at 6 months 5 participants had returned to full time work (Table 9). Education level was equally distributed among the participants. Among the participants, 38 (84%) were married or living with a partner and 7 (16%) were living alone. The most common first cardiac rhythm was VF/VT, the majority of CA events were witnessed and mean time to ROSC was 20 minutes. Participants in the present study had a predisposition for heart diseases prior to the CA. Between 1 and 6 months after the CA, 27 (60%) participants visited the health care system and of these 13 (48%) had been readmitted to the hospital. Reasons for readmission were complications/events related to the Implantable Cardioverter Defibrillator in 4 (31%) participants, chest pain in 6 (46%) and respiratory and/or abdominal symptoms in 3 (23%).

Table 9. *The table shows sex, age, social context and work situation before CA and working situation 6 months post-CA (n=45). CA= cardiac arrest.*

Sex	Age	Social context	Working situation at the time of the CA	Working situation at 6 months
16 Women	24-85 years	38 living with a partner	10 worked full time	5 worked full time
29 Men	(Mean =64)	7 living alone	6 worked part time	3 worked part time
			1 sick leave	6 sick leave
			28 retired	31 retired

Neurological outcome

All patients included (n=125) were evaluated using the CPC score. At discharge from the ICU (mean 6 days), six participants who scored CPC 3 at discharge from ICU improved to CPC 1 and one participant who scored CPC 4 improved to CPC 2 at 6 month. Functional outcome improved between 1 and 6 months ($p=0.003$). A Friedman test revealed that participants' CPC scores improved across the three assessment points: $\chi^2(2, N=45) = 56.673, p < 0.001$ (Table 10).

Physical outcome

ADL measured using the BI improved and differences over time in total score were observed ($p=0.01$) (Table 10). The main difficulties in ADL,

which improved by 6 months, were bathing, mobility, transfer and walking in stairs.

Cognitive outcome

Cognitive function measured using the MMSE showed improvements over time ($p < 0.001$) (Table 10). At 1 month post-CA, 17 (39.5%) participants scored < 24 , which indicates a cognitive dysfunction, but participants were classified as CPC 1-2, which indicates a good outcome and therefore continued in the follow-up study. At 6 months post-CA, five (12.5%) participants scored < 24 on the MMSE, of these two participants were classified as CPC 1 and three were classified as CPC 2. Improvements over time were predominantly seen in areas such as orientation difficulties ($p = 0.001$), recall ($p = 0.001$) and copying a figure ($p = 0.004$).

Table 10. *Demonstrating the distribution of outcome variables over time for included patients (n=45).*

	ICU discharge (mean 6 days)	1 month	6 month
CPC 1 n (%)	10 (21)	30 (67)	40 (89)
CPC 2 n (%)	25 (56)	15 (33)	5 (11)
CPC 3 n (%)	9 (20)	0	0
CPC 4 n (%)	1 (2)	0	0
CPC 5 n (%)	0	0	0
BI mean (SD) min-max		86 (23) 20-100 (n=44)	94 (16) 15-100 (n=44)
MMSE mean (SD) min-max		25 (4) 18-30 (n=43)	27 (4) 12-30 (n=43)

CPC=Cerebral Performance Categories, BI=Barthel Index, MMSE= Mini mental state examination.

Life satisfaction

Satisfaction with “life as a whole” was seen in 70% of participants (Figure 14). A majority of participants were satisfied with family life, ADL and partnership. Approximately half of the participants were satisfied with their personal economy, contacts, psychological health, leisure and work. Fewer were satisfied with their somatic health, a lower degree of satisfaction was observed in relation to sexual life. Gender differences were found in psychological health, χ^2 (df=1) =6.2, $p=0.007$, where more men than women indicated satisfaction.

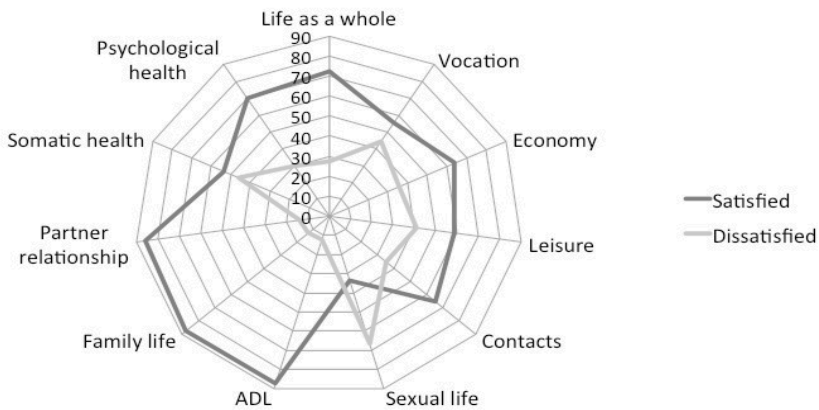


Figure 13. Variation in LiSat-11 (n=43). The figure represents the percentage of self-reported satisfaction with life (scale grades 5-6) within that certain domain. The bigger the area, the better the life satisfaction.

Paper IV

The analysis revealed three themes and ten categories were identified (Figure 15). The findings will be presented by each theme and categories.

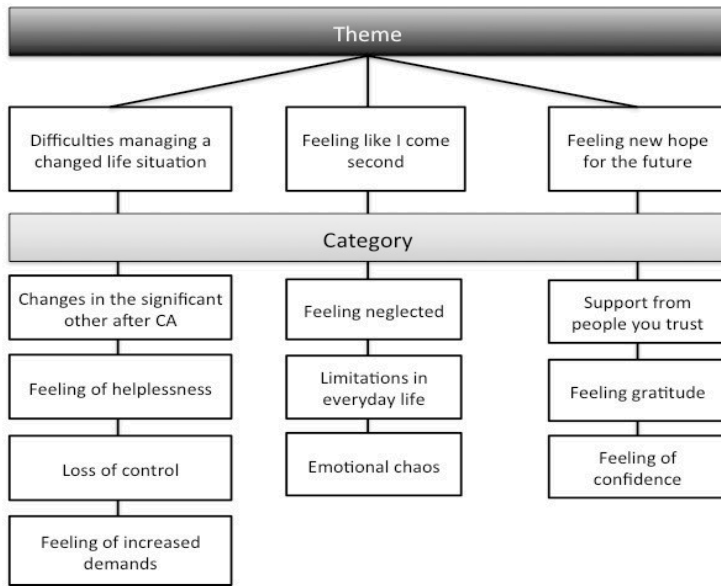


Figure 14. Illustrating the three themes and 10 categories revealed in the analysis.

Difficulties managing a changed life situation

This theme with its four categories describes a changed life situation during these 6 months after a significant other's CA. The relatives experienced that the significant other had *changed* both physically and mentally after the CA. Compared with pre-CA the significant other was clumsier and had reduced muscle strength and fitness. Also cognitive changes were described by the relatives, such as difficulties with sense of time and memory disorders and a modified personality. The relatives reflected back in time and described a feeling of *helplessness*, emotions related to the acute phase post-CA when they saw their significant other tied down with tubes at the ICU. The relatives' *lost control* over the situation because they experienced a lack of support, information, a rehabilitation plan and information on what they could expect when their significant other was discharged from hospital. During these months, relatives experienced *increased demands*: domestic responsibilities and a greater responsibility for practical matters as well for dealing with the social security system, which was burdensome.

Feeling like I come second

In this theme, three categories were identified. The relatives' described *feelings of neglecting* their own needs. They felt that all energy was spent on supporting others. They did not feel part of the surrounding world and felt that no one asked them about their needs and feelings. Further, relatives

described how they ignored their own social network and social life, which leading to a feeling of isolation. Everyday life had been *limited* because relatives reduced their working hours to part time or retired earlier than planned. For a relative who was student, studies were affected leading to a study break. The event has affected relatives *emotionally* and mentally, including sleeping disturbances and difficulty relaxing. They suffered from permanent emotional distress and fear of recurrence. Relatives found it difficult to talk about what had happened, because it made them relive the event.

Feeling new hope for the future

The third theme contained three categories. The theme comprises the need for *support*, shared feelings with others who have experienced similar events and *feelings of gratitude* to the rescue staff, healthcare personnel, friends and family. Furthermore, relatives' feelings of confidence and *hope* for the future were emerged. They expressed gratitude for life and for the fact that their significant other had survived. The family ties had grown stronger and they were closer to each other and took better care of each other.

Discussion

This work focused on post-CA care in the ICU and the overall aim was to evaluate prognostic tools, investigate neurological outcome and relatives' experiences in everyday life 6 months after the event. The findings showed that a cerebral oxygenation values obtain from the jugular bulb catheter at selected time points during and after TTM 33°C is an uncertain method for predicting neurological outcome. MRI, post-CA showed that patients with poor outcome had an extensive pathological pattern in several brain regions and patients with good outcome had a pathological pattern mainly in the frontal and parietal lobes. Impairments in physical and cognitive function are common in CA survivors treated with hypothermia but tend to decrease over time. Relatives' everyday life was still affected six months after the event and is described as both physical and emotional effects.

Cerebral saturation

Using a catheter in the jugular bulb vein has been more extensive in the care of patients with head injuries and during cardiovascular surgery to optimize cerebral blood flow¹¹³⁻¹¹⁵ but has also been used as a supplement in the post-resuscitation care.^{107, 108, 116} In Paper I we describe oxygen saturation variations obtained from a jugular bulb venous catheter in relation to neurological outcome post-CA in cases where TTM 33°C was applied. Values in oxygen saturation during TTM 33°C and normal core temperature measured from a jugular bulb catheter are illustrated in Table 11.

Table 11. *Values in oxygen saturation measured from a jugular bulb catheter during TTM 33°C and normal core temperature*

	TTM 33°C	Normal core temperature ≥36°	P-value Between temperatures
SjvO ₂	67 (60-74) (n=72)	73 (66-79) (n=69)	≤0.001
ScvO ₂ -SjvO ₂	3 (0-10) (n=72)	2 (-3-6) (n=69)	≤0.001
OEF _b	30 (23-39) (n=72)	23 (16-30) (n=67)	≤0.001

Values are presented as median and interquartile (IQR). TH= therapeutic hypothermia, SjvO₂ = jugular bulb saturation, ScvO₂ = central venous oxygen saturation, OEF_b = oxygen extraction fraction from the brain.

In the present study, patients with poor outcome tended to have higher values in the $SjvO_2$ and lower values in OEF_b at selected time points. High $SjvO_2$ values post-CA has been interpreted as poor outcome,^{107, 203} one reason for this may be that a damaged brain probably consumes less oxygen. $SjvO_2$ values below 55% are described as an ischemic threshold and were found at all time points but this did not show any differences between good and poor outcome. Although $SjvO_2$ values tended to be higher in patients with poor outcome during TTM 33°C, this was not consistent in all our observations, making it difficult to draw definite conclusions. The same applies the OEF_b values. Our results may indicate that TTM 33°C seems to have less impact on cerebral metabolism when the brain is injured by ischemia. The main findings were that values obtain from the jugular bulb catheter at selected time points during and after TTM 33°C is an uncertain and insufficient method for predicting neurological outcome in the post-CA care. The study design was prospective observational study and no intervention was performed. It is possible that the significance of the values increases if an intervention were carried out. However the balance between oxygen delivery and uptake in the brain should be of importance and need to be further investigated in the post-CA care.

Neuroimaging

To our knowledge, this is the first study describing MRI findings also in patients conscious at the time of investigation. More than half of patients survived with a good outcome.

The main findings in Paper II were that patients with good outcome had a pathologic pattern mainly in the frontal and parietal lobes. Patients with poor outcome had an extensive pathologic pattern in several brain regions. Furthermore, very low ADC values, below $600 \times 10^{-6} \text{ mm}^2/\text{s}$ were associated with poor outcome regardless of brain region. The visual image analyses and ADC measurements in pre-specified areas may contribute with valuable information to the prognostication and possible rehabilitation of CA survivors with good outcome at hospital discharge. Changes in the brain post-CA are affected by several factors such as patient age,^{204, 205} time to ROSC, and co-morbidity and are region dependent,²⁰⁶ these factors may also affect cognitive function. In the present study, 32 (57%) survived with a good outcome, i.e. CPC 1-2 post-CA. Among these patients 15 had a pathologic pattern in the brain. How this affects the patients in everyday life is not entirely investigated. These findings need to be further investigated using more specific cognitive instruments in follow-up care. It is known that CA survivors may suffer from various degrees of cognitive impairment after the event. The data varies due to different follow-up times as well as use of different

instruments to identify impairments.^{21, 148, 166, 207} In the present study, the MMSE was used at six months to describe cognitive impairments among survivors who had also been tested using an MRI. The median MMSE was 28 (24-30) in 28/32 (88%) patients who performed the test, which implies no cognitive impairments.

Neurological outcome

In Paper I-III the main focus was on investigating neurological outcome measured using CPC. The aim of Paper III was also to investigate CA survivors' physical and cognitive function over time. Among included patients, CPC improved between discharges from ICU to 6 months post-CA. However, the CPC scale is coarse and does not identify minor changes that affect the CA survivor in the home environment or at work.^{155, 156} The mRS-scale has become a complementary tool to evaluate survival post-CA.^{157, 208} The CPC and mRS scale has shown to be consistent to each other.¹⁶⁰ But neither CPC nor the mRS scale was designed for CA survivors, and they give subjective measurements that need to be complemented to meet the needs of the CA survivor.

There is a wide range of concepts and a lack of consensus over definitions and measurements in the literature on measuring patients' health and QoL. The oldest and most common concept is people's functional ability, especially in relation to performing daily activities. Other concepts are positive health, social health, subjective well-being and QoL.²⁰⁹ In Paper III we used self-report questionnaires using BI regarding functional ability and LiSat-11 regarding subjective well-being.

We found that impairment in physical and cognitive function is common in CA survivors treated with TH but tends to decrease over time. Regarding physical impairments, they did decrease over time when measured with BI. Patients predominantly reported high scores on BI which are associated with greater likelihood of being independent.^{194, 196} However the total score for BI is not the most meaningful measure, rather it is the breakdown into individual items describing specific deficiencies that is important. Used in this way, the BI might be useful as a predictor in rehabilitation.²¹⁰ Potential physical impairments revealed by the BI would also be important to inform the relatives about thus preparing them for the kinds of assistance CA survivors will need at discharge.

Cognitive impairment was investigated using the MMSE at two time points in Paper III. Cognitive impairment still remained at 6 months, particularly in orientation and memory. It is a challenge to investigate CA survivors' physical and cognitive function post-CA, as we do not have baseline data pre-CA. Cognitive impairments also exists among ST-elevation myo-

cardial infarction patients without CA and should therefore not be overstated among CA survivors.²⁰⁷ Furthermore, it is known that cognitive impairments exist in critically ill patients without brain injury after ICU admission.¹⁴⁶ Cognitive impairment probably have multiple aetiologies, such as hypoxia and hypotension, hyperglycaemia and hypoglycaemia and that patients with multi-organ failure are at risk of developing brain injury.¹⁴⁶

Despite a severe illness, which has impaired the physical and cognitive functions, 70% of CA survivors were satisfied with life as a whole. Partner, family relations and the ability to be independent in ADL seemed to be the main domains that were essential to life satisfaction. This can be interpreted as meaning that patients have recovered well. Recovery implies both clinical and personal recovery.²¹¹ Clinical recovery or rehabilitation corresponds to the professionals' prospective, focusing on reduced symptoms and increased level of function. In contrast, personal recovery concerns each person's ability to adapt to a new situation as well as to develop a new life situation.²¹¹ The LiSat-11 did not give any information on whether CA survivors wanted more of leisure or socially contacts or why they were not more satisfied with these aspects. The ability to return to work depends on patients' recovery post-CA and may affect their life satisfaction. Return to work is one way to investigate participation to society and daily functioning. But it could not be used to evaluate participation for those CA survivors who were retired. About a third of participants of working age had returned to work at 6 months. This is a lower rate compared to other studies, where about 46-79% of CA survivors returned to work during an average of 6-36 months post-CA.^{147, 207, 208, 212, 213} This may indicate that time is one important factor in CA survivors' recovery. However, the mean age at the CA event was lower in three of the previous studies (52-59 years compared to 64 years in the present study).^{147, 208, 212} The majority of participants in the present study were retired or close to retirement at the time of the CA, which may reflect the ability to return to work. Smith et al. report that the ability to return to work post-CA is also influenced by a high age at the time of the CA, whether the CA was witnessed, whether the CA was in a shockable rhythm and the cause of the CA.²⁰⁸

Time to ROSC has not been defined as a predictor of outcome, but seems to be an important factor in the resuscitation regime and in CA survivors' outcome.⁸¹ In the present study, time to ROSC was > 20 minutes in 29% of CA survivors, and in two patients time to ROSC was 50-90 minutes; all participants showed good outcomes scores at 6 months, with minor cognitive deficits. This demonstrates the difficulties involved in defining time limitations for resuscitation care.

Relatives' experiences

The main findings in Paper IV were that everyday life was still affected six months after the event. Relatives described both physical and emotional effects, mainly increased domestic responsibilities, restrictions in social life and constant concern for the person stricken by cardiac arrest. The impact in everyday life is described to continue for up to two years after the critical illness.²¹⁴ It is suggested that survivors of critical illness and their families move through five phases during recovery, each with specific needs for support during recovery.²¹⁴ Phases three-five involve preparation for discharge home, early home adjustments and late home adjustment.²¹⁴ Providing honest information about the patient's progress and outcome is important during the ICU stay as well as after discharge from hospital. Having such information makes the situation more bearable.^{152, 182}

Relatives in the present study lacked support from healthcare after discharge from the ICU and hospital, and they also experienced a decrease in provision of information. Lack of information primarily concerned contact information and support in dealing with their significant other's health after hospital discharge; this has also been described in previous studies.^{151, 152, 180} ²¹⁴ Relatives who are well prepared – in terms of having lists and instructions from physiotherapist, contact with a home care nurse and with a nurse from the cardiac clinic - are confident and not afraid to take the survivor home.²¹⁴ If the relative is confident, it may also help them feel hopefulness and find coping strategies. Relatives' ability to cope with the unexpected and traumatic event depends on their individual resources. Effective coping is associated with a strong experience of social support, earlier caring experiences and use of internal and external recourses. If these elements are missing and the person's physical/mental health is poor, the individual will have difficulty coping with the situation and coping will be ineffective.²¹⁵ Relatives' coping strategies are mainly focused on different modes of achieving emotional relief for themselves.¹⁹¹ The situation is new and very distressing when the patient is in most cases, critically ill at the ICU. When the patient is discharged from the ICU and hospital relatives' coping strategies change and they mainly concentrate their efforts on helping their significant other. Their own strength is being stretched to the limits when they need to cope not only with their own needs, but also with those of the patient.¹⁹¹ Relatives serving as caregivers for a significant other need respite care and information, but do not always ask for it. This may be because they do not wish to leave their significant other.¹⁵¹ In the present study, relatives described having neglected their own needs and reported feelings of isolation and loneliness because no one asked them about their needs and feelings. However, feelings like this gave them a sense of guilt. The interviewed relatives expressed a need for some kind of support and a need to share experiences with others, mentioning family groups as an example. Traditionally in criti-

cal care and healthcare, the main focus has been on the patient, and relatives and families have come second in terms of support and follow-up.²¹⁶ To prevent development of PTSD among relatives, different strategies should be considered, such as communication and participation in the care.²¹⁶ Visits after discharge and follow-up meetings for relatives have also been suggested to prevent mental illness.²¹⁶

Methodological considerations

The present thesis includes both quantitative and qualitative methods, which is considered to be a strong combination. The different methods provide different types of information in the area of patients' post-CA care and their relatives' experiences. The quantitative method provides results that can be measured and compared using statistics. Qualitative methods give insights into individuals' experiences and perceptions in a specific area. Furthermore, the thesis focuses on different perspectives that the ICU team encounters in the post-CA care: high technological medical care with prognostication as a main purpose (Paper I-II), and nursing care with neurological outcome among patients (Paper III) and relatives' experiences (Paper IV).

Conducting studies in clinical practice is both challenging and satisfying. It requires a great deal of time and effort to inform and motivate team members to participate and to perform medical measures outside the daily routine and furthermore, to deal with the analysis process. What makes it all worthwhile is that the results generate information that can be fed back to team members and in this case to patients and their relatives as well. There are some strengths and weaknesses that will be discussed for each paper.

Paper I

This study involved more patients than in previous published studies but had a large amount of missing data. The values and measurements from the jugular bulb catheter were only followed and not used as a treatment tool, for prognostication or for withdrawal of care. Values that are not available and that would be meaningful for analysis if they were observed are defined as missing data.²¹⁷ Missing data constitute a serious problem that undermines validity and the possibility to develop conclusions.^{197, 217} In the present study, there are several reasons why data were missing. One reason may be the study design and that there was no routine in the clinic for using the values from the jugular bulb catheter, which could have affected compliance with the study protocol. Missing data also occurred when patients died during treatment or recovered and were discharged to a medical ward before 108 hours. We included all patients regardless of missing values and did not

use multiple imputations to assign values to avoid the possible risk of differences in medical treatment between samples. The results of the analysis are described using descriptive statistic at all time points to give a better overview of the data. This may alter the results and requires awareness on possible bias. The data were not normally distributed, which made them difficult to evaluate using statistical methods. Simple univariate statistics per measurement occasion were used despite the repeated measures design, because no repeated measures model was prespecified and in order to avoid complications due to missing data. Furthermore, multiplicity issues are not a concern in this case, as the analysis is exploratory in nature and no claims were made concerning differences at specific time points.

Measuring S_{jv}O₂ also involves several potential pitfalls, such as catheter position, vein asymmetry and unequal drainage of the hemispheres. Moreover the rate of blood withdrawal from the jugular bulb catheter affects the values.²¹⁸

Paper II

Present study also describes MRI findings in patients who were conscious at the time of investigation. This may be perceived as an unnecessary and costly investigation for patients who regain consciousness. However, the visual image analyses and ADC measurements in pre-specified areas contribute valuable information to the prognostication and possible rehabilitation of CA survivors with good outcome at discharge from hospital. Manually drawing the ROIs to quantify the ADC measurements in pre-specified areas is a complement to the visual image analysis. However based on our results, ADC measurements cannot replace the visual image analysis, which requires close cooperation with experienced neuroradiologists to achieve reliability. Conducting a study in three hospitals involves several challenges and pitfalls. There were several issues that were difficult to influence, such as different MRI techniques used during the study period. That may have some influence in analyses. This was also the reason why seven patients were excluded from the quantified analysis. Another limitation of the present study is the small study population size, which is comparable to sizes in other studies, but still relatively small when looking at differences and relationships.

Paper III

An important factor and strength in the present observational study was that it followed patients over time and time assessment was uniform. We included patients who could answer at least one of the instruments at both occasions, as the aim was to analyse changes over time. Therefore patients who

did not answer the instruments at both occasions were excluded from the analyses. Both BI and MMSE are well-established and validated tools for screening for impairments occurring over time, are easy tests to perform and are not time-consuming.^{210, 219} The assessment protocol was chosen both as a self-report and face-to-face questionnaire to obtain patients' own estimation as well as an objective estimation of possible neurological deficits after CA. Participants with impaired cognitive function might have answered the questions in a false-positive way due to limitations in self-awareness. This could have been avoided by confirming their responses with a relative.¹⁹⁶ A weakness with the BI may be that a uniform cut-off value for BI has not been found, which makes it difficult to investigate any relationship between a low score on BI and MMSE. A weaknesses with MMSE may be that it is not a very sensitive test for detecting frontal lobe dysfunction in patients with preserved intellectual capacity and should not, by itself, be used as a diagnostic tool.^{219, 220} Education level and age are two other factors that can affect assessment of cognitive function.²²⁰ The loss of patients in the follow-up due to patients' health and logistic issues may have influenced the result, in that the results only reflect patients with a good outcome. However it is important to take into account that at discharge from the ICU there were nine patients who scored CPC 3-4 at discharge from ICU and who improved to CPC 1-2 at 1 month. This shows that the intention in the present study was to include patients regardless of their CPC score.

Paper IV

Trustworthiness is a concept to describe reliability and validity in qualitative research. To reach trustworthiness in Paper IV we used the four aspects: credibility, dependability, conformability and transferability developed by Lincon and Guba.^{197, 221} *Credibility* refers to how well the study measures what is intended and if the findings are congruent with reality.²²¹ Credibility was established by providing representative excerpts from the transcribed text, and by basing consensus on classifications on a large amount of data and discussions with supervisors and research colleagues. *Dependability* refers to the issue of reliability i.e., the similar results would be obtained if the work were repeated in the same context. To establish dependability a logical and clear documentation through the process was obtained and an open dialogue in the process with supervisors and research colleague was obtained. A pilot interview was performed to test the usability of the interview guide. *Conformability*, that refers to objectivity of the findings, and should reflect the participants' voice, not the researchers motivation or perspectives. To establish conformability the interviews were conducted by three ICU nurses, who contributed to a feeling of trust and safety among the relatives.^{197, 199, 221} The pre-understanding could be a weakness if the inter-

viewer assumes answers as granted. We tried to promote this by using an open dialogue with supervisors and research colleague. The four interviews conducted over the telephone were shorter in length and not as deep as the face-to-face interviews, which may have affected the data analysis.²²² However, the face-to-face interviews were so extensive that they were considered to compensate for the more shallow nature of the telephone interviews. *Transferability* means that information from the field can be transferred to or be applicability in other illness situations. This was established by the amount of included relatives (n=20) which were considered sufficient given the variation in the participants' demographic characteristics. The study sample did not include relatives who did not speak or understood Swedish, which is a limitation and could affect transferability. The findings cannot be generalized to or encompass all concerns of relatives of significant others who have survived CA, but with the knowledge available today on the topic, they can be transferred to relatives experiencing ICU care in general.^{197, 199}

Conclusion

The results from the studies shows that post-CA care is complex. The results have increased knowledge about the investigated prognostic tools, function and life satisfaction among CA survivors, as well as relatives' experiences after the event.

- The use of a jugular bulb catheter to describe variation in cerebral oxygenation showed that patients with poor outcome tend to have higher levels of $SjvO_2$ and lower levels in OEF_b at selected time point post-CA (I).
- Values obtained from the jugular bulb catheter are an unreliable method for predicting neurological prognostication (I).
- Using MRI post-CA showed that patients with poor outcome had an extensive pathological pattern in several brain regions. It was also illustrated that patients with good outcome had a pathological pattern mainly in the frontal and parietal lobes (II).
- Very low ADC values below $600 \times 10^{-6} \text{mm}^2/\text{s}$ were associated with poor outcome regardless of brain region (II).
- Impairment in physical and cognitive function is common in CA survivors treated with TH, but tends to decrease over time (III).
- Low scores on the CPC and high scores on the BI and MMSE, indicate that these instruments may be valid and complement each other, and furthermore be able to show a change over time (III).
- Lack of information from the healthcare system regarding information and a rehabilitation plan was an important area for relatives (IV).
- Relatives felt neglected, but also neglected their own needs in everyday life when a significant other had survived CA (IV).

Clinical implications and future research

Based on the findings from the present studies, a number of suggestions for clinical practice, follow-up and rehabilitation of CA survivors and their families can be made.

- Based on the results in Paper I, the use of a jugular bulb catheter is of less importance if no intervention is carried out.
- Information from the MRI is important in patients with good outcome, because it may provide some explanations that can help and guide rehabilitation. Information from the MRI can also be used when informing the patient and family about the cognitive consequences.
- There is a need to reach a consensus on which of the instruments that best reflect neurological and physical function post-CA.
- Rehabilitation plans need to be specified based on the CA survivors needs.
- The verbal information given to relatives needs to be complemented with written information, and the verbal information needs to be repeated.
- A better understanding of relatives' needs after hospital discharge could lead to improvements in information and support, which in turn could help relatives in their everyday lives.

In a future perspective, additional knowledge about post-CA care, CA survivors and their relatives is needed and new questions have been raised. Some suggestions for further research in the area are presented bellow.

- Evaluating a non-invasive method for assessing cerebral metabolism during TTM 33°C and normal core temperature.
- Further investigations in patients with good outcome using MRI and evaluate more specific cognitive instruments earlier in the follow-up care.
- Increase our knowledge about how we can identify and evaluate patients that are in need of rehabilitation.

- Investigate and evaluate the need of a follow-up visit for relatives to give the opportunity to discuss their own worries and to clarify issues that would help them to processing the event.

Svensk sammanfattning (Swedish summary)

Överlevnaden efter hjärtstopp är fortfarande låg trots att överlevnaden under 2000-talet har fördubblats. Detta innebär att sjukvården behöver öka kunskapen kring prognosbedömning under tiden på intensivvårdsavdelningen men även vad gäller patienters funktion och livskvalitet efter hjärtstoppet.

Syftet med avhandlingen var att undersöka två olika metoder för prognosbedömning under intensivvården dels genom att mäta syresättningen i hjärnan under och efter hypotermibehandling, identifiera skador i hjärnan med magnetkamera undersökning, bedömning av patienters fysiska och kognitiva funktion sex månader efter hjärtstoppet samt belysa närståendes erfarenheter vid sex månader.

Delstudie I

I delarbete I beskrivs den prognostiska betydelsen av att mäta syresättningen i hjärnan genom att analysera blod från hjärnan hos hjärtstoppsoverlevare under och efter inducerad sänkning av kropps temperatur till 33°C. Resultatet visar att syresättningen är högre hos patienter som avlider eller överlever med en dålig neurologisk funktion. Även en stor del av de patienterna som överlevde med bra neurologisk funktion påvisade höga värden under kylbehandlingen. Det är därför tveksamt om denna metod kan användas i prognosbedömningen.

Delstudie II

För att ytterligare öka kunskapen kring prognosbedömningen har i delarbete II hjärtstoppsoverlevares hjärna undersökts med magnetkamera 4-5 dagar efter hjärtstoppet. Visuella granskningar av undersökningarna utfördes och sammanställdes även kvantitativa mätningar över förutbestämda områden i hjärnan utfördes. Den visuella granskningen visade att akuta förändringar förekom hos drygt hälften av patienterna. Dessa förändringar påverkade främst den grå substansen och hjärnbarken. Ju fler förändringar i fler områden i hjärnan associerades med dålig neurologisk funktion efter hjärtstoppet. Analysen av den kvantitativa mätningen visade att låga mätvärden är vanligare hos patienter med dålig prognos men tydliga skillnader kunde endast påvisas i nackloberna. En fjärdedel av hjärtstoppsoverlevarna och

som utförde ett kognitivt test 6 månader efter hjärtstoppet påvisade en kognitiv nedsättning.

Delstudie III

Delarbete III beskriver patienters neurologiska funktion (CPC), aktiviteter i dagliga livet (ADL), kognitiva funktion och livstillfredsställelse, vid 1 och 6 månader efter hjärtstoppet. Resultatet visar att försämringar i fysisk och kognitiv funktion är vanligt hos patienter som överlevt ett hjärtstopp och som kylbehandlats men förbättringar ses över tid. Inom ADL förbättrades förflyttning och att gå i trappor. Den kognitiva förmågan var påverkad men även här sågs en förbättring över tid. När patienterna bedömde sin livstillfredsställelse själva 6 månader efter hjärtstoppet uppskattade 72.5% tillfredsställelse med livet som helhet.

Delstudie IV

I det fjärde arbetet (IV) intervjuades 20 närstående med fokus på hur vardagen påverkats 6 månader efter patientens hjärtstopp. Intervjuerna analyserades med kvalitativ innehålls analys. Närstående beskriver att de 6 månader efter sin anhörigs hjärtstopp upplevde ett ökat ansvar och ökade krav i familjen och hemmet. De upplever sig bortglömda av omgivningen trots att de haft ett bra stöd av familj och vänner. De känner sig bortglömda av sjukvården och saknar information, kontakt uppgifter, uppföljning och rehabiliteringsplaner. Mitt i all kaos som de upplever att de fortsatt befinner sig i beskriver de närstående att de känner hopp för framtiden och en tacksamhet att den anhörige överlevde hjärtstoppet.

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