

Assessment of neurological prognosis after cardiac arrest

Clinical and neurophysiological aspects

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UNIVERSITY OF GOTHENBURG

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Allting börjar med frågan varför.

Nils-Åke Svensson
Lärare i kemi och fysik

Till min familj.

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Clinical and neurophysiological aspects

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ABSTRACT

Background: Post-resuscitation care after cardiac arrest in adults includes targeted temperature management (TTM) to mitigate secondary brain injury. The recommended target temperature is between 32°C and 36°C after a large, international, randomized trial showed comparable outcomes (33°C vs. 36°C). Neurological prognostication is an essential part of post-resuscitation care, where clinical neurologic examination, including pupillary light reflex, is the cornerstone. Neurophysiologic methods such as electroencephalogram (EEG) and somatosensory evoked potentials (SSEP), are often used because of their relative insensitivity to other organ failures.

Aim: The aim was to evaluate a clinical routine change in TTM from 34°C to 36°C (Paper I) and prognostic accuracy, as well as the interrater agreement of standardized EEG patterns (Paper II). Additionally, we described how the information in written EEG reports is perceived by intensive care unit (ICU) clinicians assessing neurological prognosis (Paper III). The study protocol is provided for an ongoing study focused on describing possible interrelationships between the neurological pupil index (NPi) and SSEP (Paper IV).

Methods: The first study was a retrospective, before-and-after, observational study that included out-of-hospital cardiac arrest (OHCA) patients admitted to the central-ICU, Sahlgrenska University Hospital, either 2010 or 2014. The EEG studies (Papers II and III) were retrospective and included OHCA patients evaluated with EEG, during the period 2010–2014. The EEG

recordings were reviewed by three clinical neurophysiologists and classified according to standardized EEG pattern categories (“highly malignant”, “malignant”, and “benign”), and the pattern category was compared with patient neurological performance at hospital discharge (Paper II). The third study (Paper III) was an answer-sheet survey based on a fictional, cardiac arrest patient with one marker of poor neurological prognosis present. ICU clinicians at two university hospitals were presented with two types of EEG reports (plain-text and short standardized statement) and then asked to assess the neurological prognosis of the patient (“poor”, “not affected”, or “good”). The study protocol (Paper IV) describes a prospective, observational study with consecutive inclusion.

Results: The 34°C and 36°C TTM groups displayed similar survival and neurological outcomes at all time points (Paper I). “Highly malignant” patterns were 100% specific for poor prognosis, whereas many survivors had a “malignant” pattern. The interrater agreement varied between kappa 0.62 and 0.29 (Paper II). The standardized statement “highly malignant EEG pattern present” was associated with a higher proportion of correct identification of poor prognosis by clinicians as compared with the descriptive plain-text reports (Paper III). The study protocol (Paper IV) will include all post-cardiac patients evaluated with pupillometry, including NP_i, and SSEP, at >48 h after cardiac arrest. The ability of NP_i to predict an absent SSEP response and their prognostic accuracy for poor outcome will be calculated based on neurological performance at hospital discharge.

Conclusion: Either 34°C or 36°C can be used for TTM at our department with sustained patient outcomes. “Highly malignant EEG patterns” are highly specific for poor prognosis and the clinical value of the EEG report might be improved by clearly stating the presence of such patterns. If specific NP_i thresholds can predict the absence of SSEP response, a bedside NP_i measurement can be used as a proxy for SSEP testing. In certain patients, SSEP can be excluded to save resources during multimodal prognostication after cardiac arrest.

Keywords: cardiac arrest, neurological prognosis, prognostication, electroencephalography, somatosensory evoked potentials

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SAMMANFATTNING PÅ SVENSKA

I Sverige rapporterades det ca 6000 fall av hjärtstopp hos vuxen, som inträffat utanför sjukhus, in till det nationella registret 2019. Cirka en femtedel av patienterna överlevde till sjukhus och fick fortsatt vård på intensivvårdsavdelning (IVA). Oftast hålls patienterna nedsövda och får andningshjälp via respirator. Hjärtstoppet ger en syrebrist och cellerna i hjärnan börjar ta skada efter bara några minuter. För en del patienter är skadan mycket liten, de återhämta sig snabbt och vaknar upp när sömnmedicinerna stängs av. För andra patienter är skadan stor och ungefär hälften av patienterna som vårdas på IVA efter hjärtstopp avlider. Av dödsfallen är två tredjedelar till följd av svår hjärnskada. Men det finns också de patienter som kan vakna upp senare och återhämta sig väl. Alla som inte vaknat upp tre dagar efter hjärtstoppet undersöks noga och genomgår en prognosbedömning av hjärnans funktionsnivå.

Prognosbedömningen består av resultat från flera olika undersökningsmetoder. Bl.a. reflexer, röntgenundersökningar, hjärnaktivitetsregistrering (elektroencefalogram, EEG) och somatosensorisk reaktionspotential (SSEP). EEG mäter hjärnbarkens aktivitet via elektroder på huvudet. SSEP använder också elektroder på huvudet, men mäter istället om hjärnan tar emot känselsignaler från armen. EEG och SSEP är känsliga för störningar (brus) och signalregistreringen utförs av specialutbildad personal.

Sedan ca 20 år tillbaka används kylbehandling för att försöka minska den skada som syrebristen ger på hjärnan. År 2013 publicerades en stor internationell studie som visade att patienterna som fick kylbehandling med 33°C jämfört med 36°C hade lika stor chans att återhämta sig. Därför har många sjukhus ändrat till 36°C i sin kylbehandling efter hjärtstopp. Sahlgrenska Universitetssjukhuset ändrade sina rutiner från 34°C till 36°C år 2013.

I delarbete I jämfördes patienter som vårdades på Sahlgrenska år 2010 och 2014 med kylbehandling med 34°C och 36°C. Vi kunde inte se någon skillnad i chansen att återhämta sig eller överleva beroende på temperatur. Studien är liten, men viktig då det finns en risk att en förändring i rutin medför skillnader man inte räknat med i de tidigare kliniska studierna.

I delarbete **II** tolkade tre läkare i klinisk neurofysiologi EEG från 62 hjärtstoppsspatienter. Vi kunde visa att vissa EEG-mönster, ”högmaligna mönster”, är säkra för att förutspå dålig prognos hos patienterna. Vi såg också att samstämmigheten mellan de tre läkarna varierade.

I en vidare studie om EEG, delarbete **III**, undersökte vi hur läkare på IVA tolkar skrivna EEG-svar. Vi kunde visa att en större andel av IVA-läkarna kunde identifiera den neurologiska prognosen om de läste ett kort standardutlåtande om EEG klassen jämfört med en beskrivning av EEG mönster. Det är svårt att tolka skriven information och vissa ord kan vara laddade med visst värde. IVA-läkaren kan då få uppfattningen att prognosen är dålig, även om den inte säkert är det. Vi menar att tillägg av ett kort standardutlåtande i EEG svaret kan göra prognosvärdet tydligare för IVA-läkare.

Vår forskargrupp planerar vidare studier om prognosmetoder. Delarbete **IV** är en beskrivning av ett studieprotokoll där två prognosmetoder undersöks närmare. Den ena metoden är pupillometri som är en mätning av pupillreflexen med hjälp av en handhållen apparat och den andra är SSEP. Nervbanorna som testas med pupillometer och SSEP går nära varandra i hjärnstammen. Vi tror att undersökningsresultaten från pupillometri och SSEP kan överlappa. Eftersom SSEP är en resurskrävande undersökning, vill vi se om den enklare metoden pupillometri kan förutspå resultaten av SSEP. I så fall kan SSEP sparas till de patienter där pupillometri ger otydligt resultat. Kunskapen kan hjälpa oss att se till att våra resurser används på bästa sätt.

LIST OF PAPERS

This thesis is based on the following studies referred to in the text by their Roman numerals.

- I. Linus Arvidsson, S. Lindgren, L. Martinell, S. Lundin, C. Rylander.
Targeted temperature 34 vs 36°C after out of hospital cardiac arrest – a retrospective observational study.
Acta Anaesthesiologica Scandinavica 2017; 61: 1176-1183.
- II. Linus Lilja, S. Joelsson, J. Nilsson, S. Lindgren, C. Rylander.
Application of a standardized EEG pattern classification in the assessment of neurological prognosis after cardiac arrest – a retrospective analysis
Submitted manuscript
- III. Linus Lilja, S. Joelsson, J. Nilsson, M. Thuccani, P. Lundgren, S. Lindgren, C. Rylander.
Assessing neurological prognosis in post-cardiac arrest patients from short vs plain text EEG reports: a survey among intensive care clinicians
Resuscitation 2021; 151: 7–12
- IV. Linus Lilja, M. Thuccani, S. Joelsson, J. Nilsson, P. Redfors, P. Lundgren, S. Lindgren, C. Rylander.
The capacity of neurological pupil index to predict absence of somatosensory evoked potentials after cardiac arrest – a study protocol
Accepted for publication in Acta Anaesthesiologica Scandinavica

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ABBREVIATIONS

ACNS	American Clinical Neurophysiologist Society
BBB	blood-brain barrier
CPR	cardiopulmonary resuscitation
CPCR	cardiopulmonary cerebral resuscitation
CT	computed tomography
ECMO	extra corporal membrane oxygenation
EEG	electroencephalogram
EMS	emergency medical services
ERC	European Resuscitation Council
ESICM	European Society of Intensive Care Medicine
FPR	false positive ratio
GCS-M	Glasgow coma scale motor response
GWR	grey-white matter ratio
ICU	intensive care unit
ILCOR	International Liaison Committee on Resuscitation
IQR	interquartile range
MAP	mean arterial pressure
mRS	modified Rankin scale
MRI	magnetic resonance imaging
NPi	neurological pupil index

NPi	neurological pupil index
NSE	neuron-specific enolase
PLR	pupillary light reflex
ROSC	return of spontaneous circulation
SSEP	somatosensory evoked potentials
STEMI	ST-elevation myocardial infarction
TTM	targeted temperature management
VF	ventricular fibrillation
VT	ventricular tachycardia
WLST	withdrawal of life-sustaining therapy

KEY DEFINITIONS

Cardiac arrest	The loss of blood flow due to cardiac pump failure, leading to the loss of blood pressure and unconsciousness.
Good prognosis	Defined according to Cerebral Performance Category (1–2) and ranging from no to minor disability. Still independent in daily life.
No-flow	The state of circulation during cardiac arrest when no CPR or CPR device is used.
Low-flow	The state of circulation during CPR with limited blood flow.
Poor prognosis	Defined according to the Cerebral Performance Category (3–5) and ranging from severe disability, to coma and death.
Prognostication	The clinical evaluation of neurological prognosis based on clinical examination and other tests including neuroimaging, blood samples, and neurophysiological modalities.

1 INTRODUCTION

Cardiac arrest is a medical emergency that, when untreated, can lead to certain death. It represents both the most common natural cause of death and a medically induced state that allows cardiac surgery.

Cardiac arrest can cause pain and sorrow for the next-of-kin while also (as I have experienced) allowing a beautiful moment for the family to watch over their loved one during the process of dying.

In Sweden, ~6,000 adults are registered annually in the out-of-hospital cardiac arrest registry (OHCA) (1); however, the total annual incidence is likely higher (~10,000). The aetiology includes cardiac and non-cardiac causes, such as trauma, intoxication, and septic shock.

In addition to revascularization, care of cardiac arrest patients focuses on stabilization of vital function and attenuation of secondary brain injury. Therapeutic hypothermia was introduced in clinical routines in the early 2000s, and the latest European guidelines propose a temperature target between 32°C and 36°C; however, the optimal timing, induction method and duration, and temperature target remain unknown. The multi-centre “TTM1 trial” concluded that temperature targets of 33°C and 36°C resulted in similar patient survival and neurological outcome (2), with many centres adjusting the target temperature to 36°C based on this report.

Patients surviving the initial resuscitation and remaining comatose need intensive care and they are sedated in order to lower stress and allow therapeutic hypothermia. During prognostication, the extent of ischaemic brain injury is evaluated using multiple modalities. However, sedatives and muscle relaxants can influence neurological functions and preclude accurate clinical testing; therefore, other more robust methods are preferred.

Electroencephalography (EEG) and somatosensory evoked potentials (SSEP) have shown high prognostic accuracy with few false-positive predictions. The “highly malignant” EEG patterns have shown a specific association with poor neurological outcome. However, in clinical practice, a plain-text EEG report is issued by a clinical neurophysiologist. Thus, identification of such patterns can be difficult for the intensive care unit (ICU) clinician reviewing the report and assessing its impact on neurological prognosis.

The aim of this thesis was to evaluate whether local changes in target temperature affected patient outcomes and to further investigate the prognostic accuracy of “highly malignant” EEG patterns. Additionally, we determined how information in the EEG report is assessed by the ICU clinician, as correct assessment is crucial to neurological prognosis assessments to minimize unnecessary suffering of patients and their next-of-kin.

Furthermore, EEG and SSEP are both time- and resource intensive methods. In the study protocol, we aimed to evaluate potential interrelationships of the neurological pupil index (NPi) and SSEP in order to evaluate whether NPi can predict SSEP response in certain patients after cardiac arrest in order to optimize the use of resources in the multimodal prognostication after cardiac arrest.

2 BACKGROUND

2.1 CARDIAC ARREST

2.1.1 EPIDEMIOLOGY

Cardiac arrest incidence and survival rates vary widely depending on country, region, and reporting criteria (3-5). To facilitate uniform data reporting, the Utstein style recommendations for uniform reporting and definitions were developed for OHCA patients (6). Recent revisions have been incorporated to further facilitate comparisons between registries and reports (7, 8).

The International Liaison Committee on Resuscitation (ILCOR) investigated worldwide incidence rates, survival, and neurological outcomes in emergency medical services (EMS)-treated cardiac arrest in adults (9). The annual incidence ranged from 30.0 to 97.1 per 100,000 individuals and survival and favourable neurological outcome measured at hospital discharge or at 30-days ranged from 3.1% to 20.4% and 2.8% to 18.2%, respectively.

The first registered rhythm is an important factor and influences treatment options and outcomes. Cardiac arrests with ventricle tachycardia (VT) and ventricular fibrillation (VF) are common in patients with heart disease: however, the proportion of patients found with VT/VF is in decline and now ranges from 6.5% to 37.8% internationally (9-13). If the initial rhythm cannot be promptly recorded, the VT/VF might change to asystole or pulseless electrical activity, which represents rhythms that are “non-shockable”, and cannot be treated with defibrillation. Non-shockable rhythms are associated with worse patient outcomes (1, 14). Patients with a non-shockable initial rhythm have a low chance of survival, even if it progresses to a shockable rhythm (15).

The Swedish national cardiopulmonary resuscitation (CPR) registry (“Svenska HLR-registret”) monitors cardiac arrest incidence and outcomes. Observation started in the 1990s, and the registry is almost at 100% coverage for cardiac arrest patients where CPR is initiated. Overall, survival has increased from 4.4% since the start of observation to 11.0% in 2019. A higher survival rate is, in general, found in male patients and in patients with an initial shockable rhythm.

2.1.2 AETIOLOGY

The cause of cardiac arrest can be cardiac or non-cardiac. The most common cause of cardiac arrest is obstruction of coronary blood flow which causes myocardial ischaemia, electrical conduction-system malfunction or pump-function failure, leading to VF or tachyarrhythmia. Aetiology includes but is not limited to acute coronary disease, congenital arrhythmias, structural heart disease, respiratory failure, toxics, airway obstruction, pulmonary embolism, trauma, shock, and metabolic anomalies (13, 16).

Myocardial infarction due to coronary occlusion accounts for ~50% of all cardiac arrests according to OHCA data (17-19). However, using stricter definitions of cause and disregarding “presumed cardiac” as a feasible cause results in lower proportion of cardiac causes (28%) (13).

2.2 POST-CARDIAC ARREST SYNDROME

This syndrome summarizes the critically ill post-cardiac arrest patient (Fig. 1) and includes reperfusion brain injury, post-arrest heart dysfunction and systemic ischaemic–reperfusion response. This syndrome does not develop in all post-cardiac arrest patients and varies along with the duration of no-flow. Death due to circulatory failure is common during the first days after arrest; however, ~65% of OHCA patients succumb to hypoxic brain injury (16).

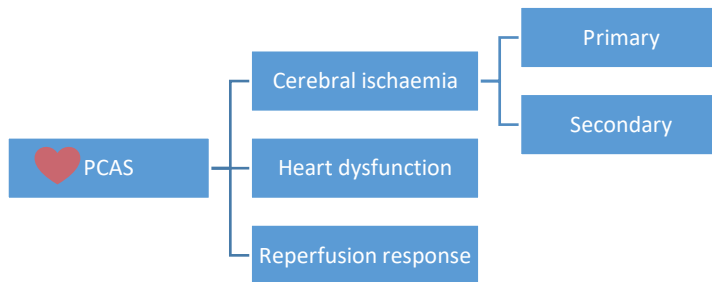


Figure 1. The post-cardiac arrest syndrome (PCAS).

2.2.1 CEREBRAL ISCHAEMIA IN CARDIAC ARREST

The brain accounts for ~20% of the total oxygen consumption, making it susceptible to ischaemic injury. The process of neuronal injury during and after cardiac arrest is complex and has yet to be described in a pure cell model (20). Neuronal injury associated with cardiac arrest can be divided into primary and secondary injury where primary damage occurs during circulatory collapse, and secondary damage occurs in the post-cardiac arrest phase after return of

spontaneous circulation (ROSC). Additionally, secondary injury is caused by delayed neuronal death and can be worsened by other potential stressors.

When the heart arrests, cerebral circulation ceases immediately causing global ischaemia. Neurons are dependent on continuous glucose and oxygen delivery in order to maintain cell metabolism and membrane potential via the ATP-dependent $\text{Na}^+\text{-K}^+$ pumps. Cell ATP level is depleted within minutes of cardiac arrest, which disrupts membrane integrity and causes anoxic depolarisation, intracellular Ca^{2+} inflow, and glutamate release leading to cellular oedema. If blood flow is not restored, the cells become oedematous and undergo necrosis. Prolonged ischaemia results in loss of blood-brain-barrier (BBB) patency, causing further brain oedema (21).

After ROSC, secondary brain injury can occur from reperfusion injury, including inflammation, formation of free oxygen radicals, excitotoxicity, reactive hyperaemia, and cerebral oedema (20, 22). In the post-cardiac arrest patient with sustained ROSC, cerebral autoregulation is impaired which can result in sustained tissue hypoxia and ischaemia (21). Moreover, some areas of the brain can experience low or no blood flow despite increases in total cerebral blood flow and otherwise adequate perfusion pressures. However, there is significant variation. A previous report described a patient with intact autoregulation and cerebral tissue hypoxia upon mean arterial pressure (MAP) falling <110 mmHg, whereas another patient showed no hypoxia at any MAP >75 mmHg (20). One proposed mechanism is tissue swelling that causes capillary constriction along with activation of tissue factor and fibrin, resulting in capillary occlusion (21, 23).

Fever and status epilepticus are other factors associated with increased mortality due to secondary brain injury (22). Generalized cerebral oedema can occur either early or late and is, regardless of timing, a dismal sign (20). Furthermore, there are several care-related factors that can worsen brain injury, including poor glucose control, low MAP, hyperventilation with hypocapnia and cerebral vasoconstriction, hyperoxaemia (which may increase free oxygen radicals), and too early withdrawal of life sustaining treatment (WLST) (16, 17, 22).

2.2.2 POST-ARREST HEART DYSFUNCTION

The loss of myocardial perfusion during arrest leads to myocardial dysfunction (often referred to as “myocardial stunning”), which represents a global heart phenomenon that contributes to further pump failure and early circulatory death after cardiac arrest; however, this condition is usually reversible and

responds well to inotropic drugs (24). In an animal study, a 15-min arrest caused the left ventricle ejection fraction to decrease to 25% at 5 h after ROSC, although all values returned to baseline at 48 h (25).

2.2.3 THE ISCHAEMIC–REPERFUSION RESPONSE

Ischaemic–reperfusion response often manifests as a sepsis-like state with a systemic inflammatory response, intravascular volume depletion, impaired vascular autoregulation and poor oxygen delivery as a result. Hypotension, increased lactate levels, and arrhythmias are common findings. Microvascular thrombosis can occur not only in the cerebral circulation but also the peripheral circulation, with the same endogenous activation of coagulation pathways (22). If not properly managed, hypoxaemia will cause metabolic acidosis, further endothelial activation, risk for infections, and progressive organ failure.

2.3 TREATMENT PRINCIPLES

The resuscitation and treatment of cardiac arrest can be divided into separate phases: intra-arrest; resuscitation, both in- and out-of-hospital; and post-resuscitation. However, a distinct separation of the phases can be difficult. An example is therapeutic hypothermia which can be introduced in different phases and physical locations, including at the arrest site, in the ambulance, in the emergency room, during revascularization, or in the ICU. However, the overall management of cardiac arrest patients follows the chain of survival (Fig. 2). Figure 2 presents the phases in the chain of survival, and the recommended cause of action in each phase is summarized in the international guidelines.

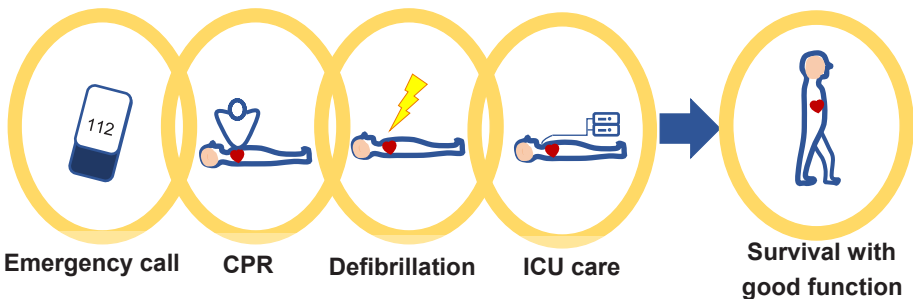


Figure 2. The chain of survival

The European Resuscitation Council (ERC) and European Society of Intensive care Medicine (ESICM) guidelines are updated every ~5 years for all aspects of cardiac arrest care (from infants to adults). The latest versions were published in 2015 (26-36) and the updated versions are currently available for public comment (37).

2.3.1 HISTORY OF CARDIOPULMONARY RESUSCITATION IN ADULTS

Several resuscitation techniques have been used and were first developed with the intention of saving a person from near drowning. The barrel method is well known among early methods and involves placing the person face down on an overturned barrel. This allows them to be rolled back and forth, thereby promoting ventilation via chest compression and decompression. In the horse back method, the person was instead placed lying face down over the back of a horse, and as the rescuer ran alongside the horse, compression–decompression ventilation was established. Later, the Leroy method in the 1820s was the first resembling modern CPR. The patient was placed in supine position, and the rescuer compressed the chest and abdomen in sequence.

In hospitals, cardiac massage was conducted via the open chest, abdominal transdiaphragmatic and abdominal subdiaphragmatic routes. The latter two were considered faster, and the resuscitation success rate was reportedly ~25% (38). The closed-chest cardiac massage approach later described by Kouwenhoven and colleagues, suggested that cardiac resuscitation could be initiated by “anyone, anywhere” (39). The modern CPR was born. However, it would take several decades before efficient ventilation methods were studied.

In the 1930s, the chest-compression and arm-lift techniques were used. In these methods, the patient was placed face down while the rescuer alternated between compression on the back of the chest, followed by lifting the arms of the patient, resulting in expiration and inspiration, respectively. This is referred to as the “Holger Nielson” method and is still used according to the American Heart Association.

Peter Safar, the “father of modern cardiopulmonary resuscitation”, is a late professor of resuscitation medicine that conducted studies on jaw thrust and mouth-to-mouth ventilation. He also studied hypothermia in dogs as he firmly believed hypothermia would improve neurological recovery after cardiac arrest. Mild hypothermia was included in his proposed cardiopulmonary cerebral resuscitation (CPCR) method. But he later feared that CPCR would be used without exception on all patients and thoughtfully advised that, “CPCR is for the person with a brain and heart too good to die.”.

In Sweden, Stig Holmberg was among the most important people associated with the development of CPR and cardiac arrest care. He worked as a cardiologist in Gothenburg and helped establish the cardiac care wards at the Sahlgrenska University Hospital. He was also engaged in teaching CPR to the

public, with his goal being that CPR should be as commonly known as swimming. In the early 1970s, he launched an EMS service (the “OLA” ambulance) that was an ambulance unit with specialized personnel capable of responding to life-threatening situations. The unit comprised two EMS personnel and a nurse from the cardiac ward. Additionally, Dr. Holmberg also laid the foundation to the Swedish national CPR registry.

2.3.2 EMERGENCY CALL AND CPR

The care of a cardiac arrest patient starts with recognition of symptoms and cardiac arrest, as the sooner the condition is recognized, the EMS alerted, and CPR initiated, the better. CPR with good quality compressions and ventilation at a 30:2 ratio ensures low-flow circulation, minimize the ischaemia, and buys time for the EMS to arrive.

Manual CPR given by a bystander or professional improves survival and neurological outcomes (40). Ideally, several rescuers can execute CPR by alternating the person supplying chest compressions every few cycles. The quality of CPR is important, and pauses should be kept to a minimum in order to increase the chance of survival (41). CPR reportedly increases the VT/VF duration and, therefore, the possibility to defibrillate. At best, CPR can provide 30% of normal cerebral and coronary blood flow (27).

There are two models explaining circulation during CPR: “the cardiac pump” and “the thoracic pump” models. The cardiac pump model is purely mechanical, as the blood is forced out of the heart during closed-chest massage as the heart is compressed between the anterior and dorsal thoracic wall and the vertebrae (39, 42). By contrast, the thoracic pump model relies on a change in intrathoracic pressure during CPR. Most likely both models are in simultaneous interplay and influenced by ventilation and the depth of chest compressions, with uncertain relative interrelationships (43).

Several CPR devices exist, including the Lund University Cardiac Assist System (commonly known under the acronym LUCAS), the LifeBelt, and the AutoPulse. These devices can relieve the fatigued rescuer applying CPR, minimize CPR pauses, and deliver compressions with consistent depth. Although feasible and currently used (44-46), a recent Cochrane review concluded device CPR to be similar to manual compressions in terms of survival and neurological outcomes (47). However, devices can be especially useful during prolonged CPR, interventions, transportation, and in preparation for extra corporal membrane oxygenation (ECMO) assisted CPR (47).

ECMO CPR was studied in the CHEER trial, which included 26 refractory cardiac arrest patients. ECMO was established in 24 and ROSC in 25 with survival with full neurological recovery reached in 14/26 patients. However, a systematic review of ECMO CPR delivered inconclusive results, with a low quality of evidence and a high risk of bias, which precluded a meaningful meta-analysis (48).

2.3.3 DEFIBRILLATION AND INTRA-ARREST DRUGS

Early defibrillation is an essential part of the chain of survival (Fig. 2). Defibrillation is used to “restore and restart” the electrical system of the heart. The device can be used in automated mode, where the device analyses the rhythm, or manual mode, where a caretaker can deliver a shock manually. Manual mode is often used by care teams in advanced-CPR algorithms to minimize interruptions of chest compressions.

Epinephrine has been used in the advanced cardiac life support algorithm since the 1960s. Evidence of its efficacy has been questioned and, as its use might increase the chance of ROSC but not neurologically intact survival (49, 50). A pre-hospital, double blinded, placebo-controlled study conducted in the UK randomized ~3900 patients to each treatment arm and found that epinephrine increased the chance of ROSC in patients with non-shockable rhythms as compared with those with shockable rhythms. Regarding survival, the odds were in favour of epinephrine; however, many survivors in the epinephrine group exhibited severe neurological deficits (51).

Other drugs previously studied, reviewed and meta-analysed, such as vasopressin concluded that while they might increase survival to admission, they did not increase long-term survival with good neurological function (50).

2.3.4 POST-CARDIAC ARREST CARE

In the EMS or hospital setting, cardiac arrest care follows well-established algorithms. The airway can be secured using different techniques, with intubation widely used in the Swedish EMS service and in hospital resuscitation teams. Ventilation is monitored by capnography, with PaCO₂ maintained within a normal range, and SaO₂ kept within a range of 94% to 98% to avoid hyperoxaemia. Intravenous access is secured along with circulatory monitoring via an arterial line. Hypovolaemia is treated with crystalloid fluids, and vasopressors can be used to maintain a systolic blood pressure >100 mmHg (26).

When a spontaneous pulse-bearing rhythm has been established, the ABCDE approach is used to find and treat potential reversible causes. These are referred to as the “4Hs/4Ts” and include hypoxaemia, hypovolaemia, hypo-/hyperkalaemia, hypo-/hyperthermia, thrombosis (heart or lung), tension pneumothorax, tamponade, and toxins (27).

A 12-lead electrocardiogram, cardiac echo, angiography, and revascularization are important early on, especially to find and treat ST-elevation myocardial infarction (STEMI). However, no survival benefit has been found in early versus delayed (>24 h) angiography and percutaneous coronary intervention (PCI) for non-STEMI cardiac arrests (52).

2.3.5 POST-RESUSCITATION INTENSIVE CARE

The main focus of the post-resuscitation phase is to stabilize vital organ functions in order to facilitate neurological recovery, which is prognosticated according to evidenced procedures (Fig. 3). Intensive care includes TTM within a constant temperature of 32°C to 36°C for at least 24 h and fever prevention for 72 h. Ventilation should be established to maintain normal PaCO₂ and SaO₂ and blood glucose levels should be maintained within a normal range to ensure sufficient glucose delivery to the brain. Haemodynamic monitoring, often with invasive measures, provides continuous blood pressure, arterial blood gas with lactate level, and cardiac output and index measurements. Urine output should be normal (0.5–1.0 ml kg⁻¹) (26).

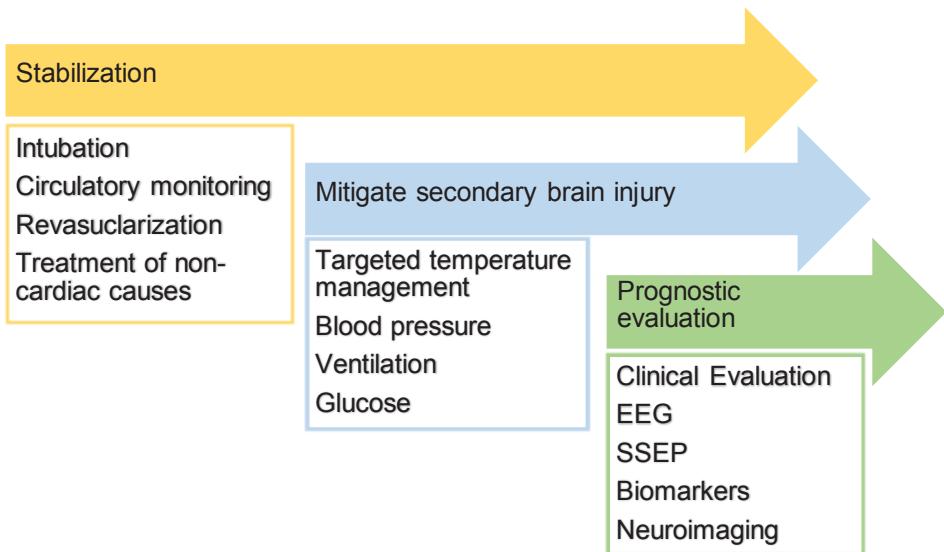


Figure 3. Schematic illustration of post-resuscitation care.

2.3.6 THERAPEUTIC HYPOTHERMIA

Hypothermia as a treatment option was first evaluated in cell and animal models. Studies on dogs showed prolonged tolerance of circulatory arrest with post-arrest cooling (53, 54), and another study reported that metabolism in human brain cells was suppressed during hypothermia (55).

Two important trials were published in 2002 (56, 57) and hypothermia therapy was ultimately introduced into clinical practise according to these trials which found positive effects on survival and neurological outcome. Temperature targets were low (32–34°C). A contributing factor to the positive effects was thought to be fever in the control groups. In a large, multi-centre, randomized trial, TTM 33°C or 36°C resulted in similar survival rate and neurological outcome at 180 days (2). Nevertheless, a no-fever approach was unexplored. As a follow up, a new trial comparing the efficacy of use of TTM 33°C to strict fever control (normothermia, <37.5°C) was initiated, with results yet to be published (58).

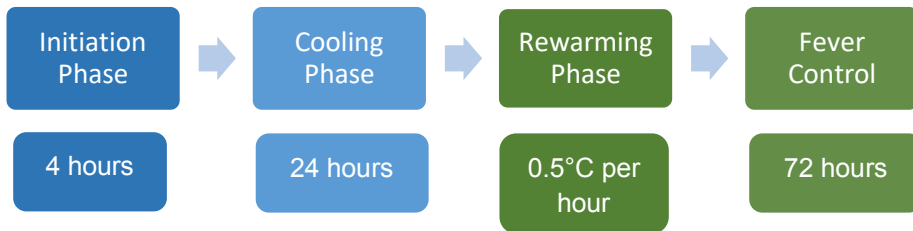


Figure 4. Schematic overview of TTM strategy.

Many approaches to TTM have been evaluated. Theoretically, earlier application of TTM can result in better outcomes. A previous study showed that application of cold intravenous fluids did not decrease the time to target temperature (59), and trans-nasal cooling showed shorter time to reach target temperature (34°C) although no benefit survival or neurological outcome (60).

Some sub-sets of patients might benefit from lower TTM temperatures, as observed in those with a non-shockable initial rhythm (33°C vs. 37°C) (61). However, the differences in application and measurement of TTM might play an important role in the variable outcomes observed in clinical studies and routines. Therefore, a standard for TTM is needed to facilitate uniformity between studies (62).

2.4 PROGNOSTICATION

The main focus of this thesis was neurological prognostication, including the neurophysiological modalities, EEG, and SSEP. Both early and late prognostic markers of poor and good outcomes exist, and the timing of each modality is of utmost importance.

The Cerebral Performance Category (CPC) scale is commonly used to assess the neurological outcome of a patient (Table 1) (63). It was first developed to assess neurological outcomes after severe brain injury. The CPC has long been the primary scale used for outcome reporting in cardiac arrest studies and was recommended in previous versions of the Utstein style recommendations.

However, the modified Rankin Scale (mRS) is currently the recommended measurement of crude neurological outcome (Table 2), as it demonstrates better resolution regarding neurological performance and differentiation between dependant and independent patients with moderate disability. However, both scales lack measurement of patient-reported outcomes, which are more frequently used in randomized trials. A subjective patient report can be used to screen for impaired cognitive function in routine practice (64, 65).

Table 1. The CPC scale and definitions of neurological outcomes used in this thesis.

Dichotomization of neurological outcome	Neurological performance
Good outcome	CPC 1. Good performance. No or mild psychological or cerebral deficit, such as memory problems.
	CPC 2. Moderate disability. Independent in daily life. Able to work in sheltered environments.
Poor outcome	CPC 3. Severe disability. Dependent on others in daily life activities.
	CPC 4. Coma or unresponsive wakefulness syndrome.
	CPC 5. Death.

Table 2. The mRS and the definitions of neurological outcomes used in this thesis.

Dichotomization of neurological outcome	Neurological performance
Good outcome	mRS 0. No symptoms or deficit.
	mRS 1. No significant disability. May have some symptoms but can do all daily activities.
	mRS 2. Slight disability. Unable to all previous activities but is able to look after own affairs.
	mRS 3. Moderate disability. Requires help but is able to walk without assistance.
Poor outcome	mRS 4. Moderately severe disability. Unable to attend to own bodily needs and unable to walk without assistance.
	mRS 5. Severe disability. Bedridden, incontinent and requiring constant nursing care.
	mRS 6. Death.

2.4.1 PREDICTING POOR OUTCOME

The prognostication modalities in the multimodal neurological prognostication after cardiac arrest are designed to identify features firmly associated with poor neurological outcomes. If no such features are found, the prognosis can be regarded as indeterminate, and the patient is re-evaluated while kept on life support. Generally, sufficient time must be allowed for sedation washout and neuronal recovery after ischaemia and hypothermia. The ERC/ESICM guidelines summarize current evidence and expert opinions (26). The recommended prognostication modalities are clinical evaluation, biomarkers, neurophysiological methods, and neuroimaging. The presented evidence refers to studies on patients treated with TTM when not specified otherwise.

The proposed algorithm from the 2020 ERC/ESICM is presented in Figure 5 (37). The main changes from the previous version were removal of the separate 72- and 96-h criteria, and the addition of Glasgow coma scale motor response (GCS-M) 3 as an entry criterion. The presence of two or more criteria determines the likelihood of a poor outcome; however, the ICU team needs to pay attention to discordant signs regarding prognostic test results.

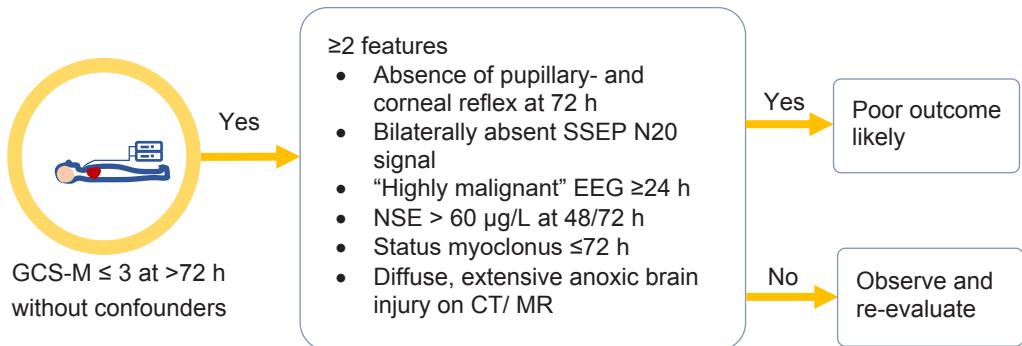


Figure 5. The prognostication algorithm proposed in the 2020 ERC/ESICM draft guidelines.

2.4.2 CLINICAL FEATURES

Clinical examination is the core modality of prognostic assessment. Pupillary light reflex (PLR) and absent motor response were evaluated for prognostic use in the 1980s (66). Later, status myoclonus with early debut (<24 h) and absent corneal reflex were identified as predictive of poor prognosis (67). Currently, absence of or extension response to pain ≥ 72 h after ROSC is predictive of poor outcome, although the false positive rate (FPR) is high (27%, range 12–48%) (26). Notably, there are numerous equally likely causes of a lack of motor response, including lingering sedative effects or neuromuscular blockade.

2.4.2.1 Light reflex

Bilateral absence of PLR and corneal reflex remain highly predictive of poor outcome, (FPR, 1%; range 0–3) (26); However, both can be caused by sedatives. Recent studies on PLR assessed by a pupillometer reported promising results in neurological prognostication after cardiac arrest (68, 69). The pupillometer provides several values, including the Neurological Pupil index (NPI). Figure 6 shows a schematic of the standard PLR test using a flashlight and the pupillometer, which measures PLR using a standardized light flash and infrared light.

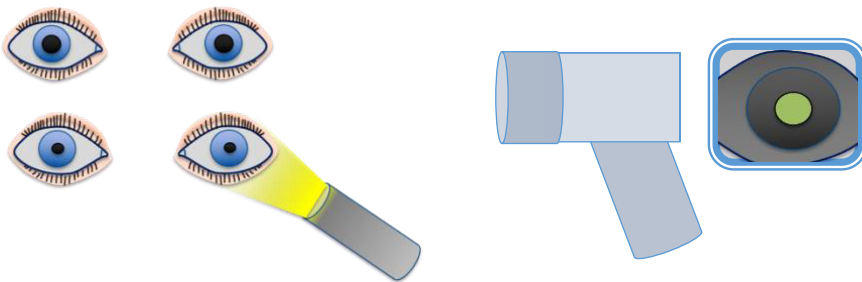


Figure 6. Schematic of PLR (left) and use of a pupillometer (right).

2.4.2.2 Myoclonus

Myoclonus describes sudden, involuntary muscular jerks, and status myoclonus is myoclonus of prolonged duration (typically >30 min). The presence of myoclonic jerks is not invariably related to poor outcome; however, if the status myoclonus debuts <48 h after ROSC, it is highly predictive of poor outcome (FPR 0%; range 0–4) (26).

2.4.3 NEUROPHYSIOLOGY

2.4.3.1 EEG

EEG measures the cortical activity of the brain via scalp electrodes (Fig. 7) and is used in the post-cardiac arrest patient to diagnose and treat status epilepticus, as well as assess prognosis. An unreactive EEG is defined as the EEG background being unresponsive to stimuli such as sound, eye opening and pain.

Status epilepticus during TTM or after rewarming is often consistent with a poor outcome. Burst suppression can be a transient finding during TTM in survivors; however, if present ≥ 72 h after ROSC, it is firmly associated with a poor outcome (26, 70-72).

EEG patterns referred to as “highly malignant”, are predictive of poor outcome (71, 72). The patterns are defined according the terminology proposed by the American Clinical Neurophysiologist Society (ACNS) and include suppressed background ($<10\mu\text{V}$) without discharges (100% suppression), suppressed background with continuous periodic discharges, burst-suppression background with or without discharges (73). The “highly malignant” EEG patterns are part of the standardized EEG pattern categories (Westhall model) along with “malignant” and “benign” patterns. “Malignant” patterns are uncertain in prognostication whereas a “benign” or reactive EEG is indicative of a good prognosis (71, 72, 74, 75).

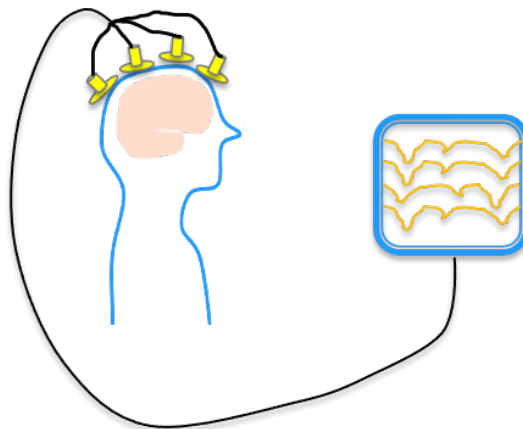


Figure 7. Schematic of EEG.

2.4.3.2 SSEP

SSEP represent the somatosensory cortex response to repeated stimulus to the contralateral median nerve. Receiver electrodes are placed on specific anatomical locations and detects a signal peak at a specific time point post-stimuli. Erb's point corresponds to the brachial plexus, N₁₃ corresponds to the cervical spine, and the N₂₀ corresponds to the somatosensory cortex (Fig. 8). A valid registration needs to be technically adequate and include each mandatory component (76). If the N₂₀ signal is bilaterally absent, SSEP shows a low FPR for poor outcome both during hypothermia and after rewarming (FPR, 0% and 1%; ranges 0–2 and 0–3 respectively) (77). Although, false-positive cases exist, they were often affected by artefacts (78). In a study with consecutive SSEP registrations for up to five days, an absent SSEP signal did not reappear over time (75). A common limitation in SSEP evaluation studies is that SSEP was often part of the WLST decision (26).

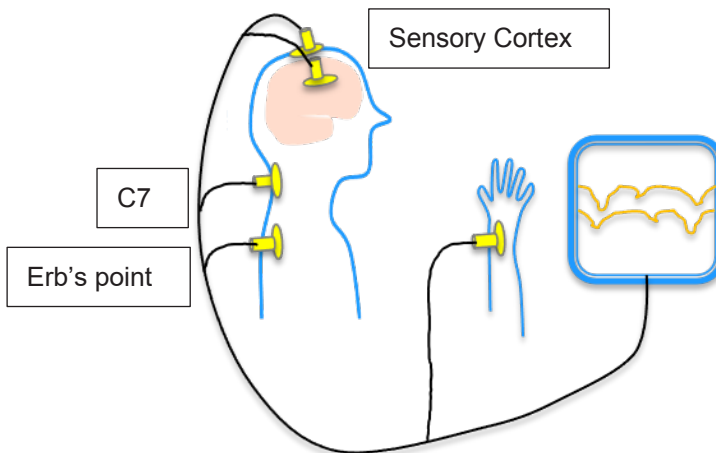


Figure 8. Schematic of SSEP registration. Stimulation of the median nerve with reading points at the brachial plexus (Erb's point), the cervical spine (C7), and the sensory cortex.

2.4.4 BIOMARKERS

Biomarkers have recently shown great potential in accurate prognostication; however, an exclusive brain-specific marker has not yet been discovered for prognostic use. Neuron-specific enolase (NSE) and S100B were both included in the 2015 guidelines; however, S100B was no longer recommended in the 2020 draft guidelines (26, 37). NSE demonstrated the best prognostic performance at 48 h to 72 h due to its long half-life and is the most widely used biomarker (79, 80). NSE is not available locally in most regional hospitals in Sweden; the sample can be sent for analysis, although transportation routines and centralized analysis can cause delayed results, which often diminishes the clinical use.

Other markers that show prognostic potential include glial fibrillary acidic protein (GFAP), Tau, ubiquitin C-terminal hydrolase L1 (UCHL1) and neurofilament light chain (NFL) (81). Tau shows higher prognostic accuracy than NSE (sensitivity for poor outcome 66%, 95% confidence interval: 61–70; FPR 2% at 72 h) (82). NFL has demonstrated better prognostic capacity than all other known modalities, with higher sensitivity at comparable specificities (80). However, NFL requires further evaluation.

2.4.5 NEUROIMAGING

Computed tomography (CT) scanning of the brain can provide differential diagnostic information, as well as prognostic information. The CT is often performed at the discretion of the treating clinician, with the optimal timing for prognostic CT theoretically later rather than early after ROSC due to the expected progression of cerebral oedema.

Generalized oedema is a grave sign of brain injury. A sub-study of the “TTM1 trial” showed that generalized oedema identified in CT scans performed <24 h, or 24 h to 7 days after arrest was highly predictive of outcome at 6 months (sensitivities: 14% and 57%; and specificity: 98%, and 100% respectively) (83).

Measurement of the grey-white matter ratio (GWR) represents a quantitative approach to prognostication in neuroimaging. In a small study, a normal GWR value was determined as 1.32 in healthy controls, while GWR was 1.19 in the poor outcome group and 1.28 in the good outcome group (84). Other studies reported cut-offs with 0% FPR for poor outcome ranging from 1.1 to 1.22; however, the method used for GWR measurement varied (85, 86).

Magnetic resonance imaging (MRI) is often preferred in the prognostication due to its spatial diagnostic resolution, as it can provide prognostic information when other methods shown normal results (87). An MRI scoring system first used for perinatal asphyxia proved feasible in prognostication of adult cardiac arrest patients (88). That system is based on individual scoring of 21 brain regions based on signal abnormality in each region, scored from 0 to 4 (ranging from a normal signal to severe signal abnormality). The scoring system was later evaluated in a prospective single-centre study and found to predict neurological outcome with a sensitivity >80% and a specificity of 100% (89). Given the rapid development of MRI, the scoring system needs to be simple and the imaging protocols standardized and easily applicable in order to allow comparison across centres (90). Although MRI results are highly valuable, their acquisition requires significant effort from the caretaking team in a post-cardiac arrest ICU patient.

3 AIMS

- I. To evaluate local changes in target temperature from 33°C to 36°C in TTM after cardiac arrest.
- II. To investigate the prognostic ability of “highly malignant” EEG patterns in post-cardiac arrest patients from a routine practice cohort.
- III. To investigate how ICU clinicians interpret neurological prognosis from a short statement versus plain-text EEG reports in a standardized cardiac arrest patient.
- IV. To design a study to investigate the interrelationships between NPi and SSEP in prognostication of comatose cardiac arrest patients.

4 PATIENTS AND METHODS

Table 3. Overview of papers included in this thesis.

Paper	I	II	III	IV
Subject	Routine TTM management	Standardized EEG patterns and interrater agreement	EEG report type and influence on prognosis assessment	Interrelationships between NPi and SSEP
Design	Retrospective, observational	Retrospective, observational	Survey	Prospective observational (protocol)
Study population	≥18-years old patients admitted to ICU after an OHCA		ICU clinicians	≥18-years old patients, all cardiac arrests
Inclusion criteria	Treated with TTM in 2010 or 2014	EEG, within 7 days of cardiac arrest	Voluntary participation	Comatose ≥48 h after ROSC and evaluated with NPi and SSEP

4.1 ETHICAL CONSIDERATIONS

The basic ethical principles of autonomy, beneficence, no maleficence, and justice are the cornerstones of clinical practice and ever present in the ICU. The goal of resuscitation and post-cardiac arrest care is the discharge of a neurologically intact and independent patient. This is the primary goal of the ICU team, although the patient and next-of-kin might have other goals and view the quality of outcome differently. Dependence on others in daily life is a wide-ranging term, and CPC 3 usually represents a “poor outcome” in most studies. However, some might consider this a good outcome that results in excellent quality of life. Therefore, it is important to gather information about the patient, their thoughts, desires and way of life. In Sweden, treatment decisions are at the discretion of the treating clinician; however, information from the next-of-kin should be taken into account.

The restriction of care and WLST are part of the normal clinical routine and no-maleficence ethics. The underlying principle is to avoid doing harm by continuing treatment if the patient has little or no chance of recovery. However, in other centres, WLST is not performed based on laws and/or ethics.

Patients still in a coma after 72 h generally have a high mortality, with the most common cause of death at that point being WLST. Therefore, the clinical decision to restrict or withdraw care should be unbiased and based on accurate testing and current evidence; however, no perfect prognostic test exists, and the treating ICU team could be biased.

All studies in this thesis have been reviewed by the local ethical committee of Gothenburg or the Swedish Ethical Review Authority. All patients or next-of-kin received information about registration in the local ICU database at the time of care. One can also request to opt-out of the database at any time without a specified reason.

In papers **I** through **III**, patients were studied retrospectively, which inferred no risk but a potential for breach of integrity. The study described in paper **IV** is a prospective, observational study. The risk of excess harm due to the study is minimized because no additional tests or treatments are planned. An informed consent will be sought from patients regaining consciousness or the next-of-kin at the appropriate time.

4.2 OUTCOME MEASUREMENTS

The main outcome measurements were survival and neurological performance. Outcome was measured at ICU discharge, hospital discharge, 30 days and 90 days (**I**) and at ICU and hospital discharge (**II** and **IV**).

We used the CPC scale to assess neurological performance (**I**, **II**, and **III**) (Table 2) (63) due to its wide use, although a limitation is the coarseness of the scale.

Paper **II** assessed patients who had a routine EEG performed. All EEG recordings were re-read and classified into the standardized categories (73), and EEG pattern category was compared with neurological outcome at hospital discharge. In **III**, we evaluated the prognosis applied by ICU clinicians from the EEG reports. The survey was based on real patients and we compared a short, standardized statement to original plain-text EEG reports. Primary outcome was the proportion of ICU clinicians that correctly identified a poor neurological prognosis from the EEG reports consistent with a “highly malignant” EEG. Additionally, we described the prognosis applied by the ICU clinicians from the EEG reports consistent with “malignant” and “benign” pattern categories.

In the study protocol (**IV**) outcome will be assessed at hospital discharge according to the mRS (Table 3) (91, 92). The prognostic accuracy of NPi and SSEP will be measured as sensitivity and specificity for poor outcome. The cut-off value of NPi to predict an absent SSEP response with <5% FPR will be calculated using a receiver operating curve (ROC).

4.3 PAPER I

Objective: To investigate whether a change in target temperature from 34°C to 36°C resulted in a change in survival and neurological outcome.

Background: After participating in the “TTM1 trial” 2011–2013, the Sahlgrenska University Hospital changed the targeted temperature from 34°C to 36°C. We used this change to evaluate whether patient outcomes differed between the two target temperatures.

Design & patients: Before and after, observational cohort study, using data from the medical records and observational charts. Patients from 2010 and 2014 were screened and those eligible were all adults (>18-years old), with a cardiogenic OHCA who received post-resuscitation care at the Sahlgrenska University Hospital ICUs. Primary outcome was survival and neurological function as measured by CPC at different time points: ICU discharge, hospital discharge and at 30 and 90 days. We analysed the primary outcome using chi-squared tests.

4.4 PAPERS II AND III

Objective: Paper II – to determine the prognostic accuracy of “highly malignant” patterns and the interrater agreement amongst three clinical neurophysiologists in a routine practice patient cohort. Paper III – to describe how short, standardized EEG statements and plain-text EEG reports influence ICU clinicians’ assessment of neurological prognosis in a standardized cardiac arrest patient.

Background: In 2014, three standardized EEG pattern categories were proposed, based on the ACNS terminology for EEG in the ICU (73, 93). The categories were “highly malignant”, “malignant” and “benign” patterns. The “highly malignant” patterns included EEG patterns thought to always be associated with poor outcome. Later studies on sensitivity, specificity and interrater agreement for the pattern categories were published (72, 94).

The term “malignant” applied to an EEG pattern description could be troublesome because of the potential inference induced by the term and influences from other conditions and diseases. This is especially the case when the prognostic accuracy of “malignant” patterns is low.

Design & patients: An observational, non-intervention cohort design (II) and a survey (III). Both papers include patients treated at the Sahlgrenska University Hospital from 2010 to 2014, all of whom were adults (>18-years old) and resuscitated from OHCA. All included patients were evaluated with a routine EEG during the post-resuscitation care, at the latest seven days after ROSC (II) or at any time (III). If a patient had several EEG registrations within seven days, the EEG addressing the clinical question of prognosis was chosen. In patients with consecutive recordings during coma, the last recording was chosen.

The EEGs were re-read by three clinical neurophysiologists and classified according to the standardized pattern categories. Raters were blinded to the assessment of the others, to all clinical information and patient outcome. In case of non-consensus, the most pessimistic pattern was used (II). The pattern categories were compared to patient outcome (II) and sensitivity, specificity and interrater agreement were calculated.

The survey (III) was conducted in two university hospitals. The ICU clinicians who volunteered were given written information (Appendix), a survey, and an answer sheet. They were advised to assess the prognosis of a fictional, standardized patient presenting one factor consistent with poor prognosis (elevated NSE level). The survey included a purposeful sample of 17 original plain-text EEG reports and three standardized short statements. The short statements simply stated that a “highly malignant”, “malignant” or a “benign” EEG pattern was present.

The ICU clinicians read the EEG reports and noted their assessment of the neurological prognosis (“poor prognosis”, “prognosis not affected” or “good prognosis”). Their prognostic accuracy was compared with the prognostic value of the corresponding EEG according to the standardized EEG pattern category, as assigned by a majority of three clinical neurophysiologists. Primary outcome was the proportion of correct assessments from the original plain-text reports versus the short statements. Correct prognostic assessment was defined as four out of five of the plain-text reports identified as “poor prognosis” and the identification of the short statement “highly malignant pattern present” as “poor prognosis”.

4.5 PAPER IV

Objective: To describe the interrelationships between NPi and SSEP in comatose post-cardiac arrest patients.

Background: Both the PLR and SSEP are robust methods for predicting poor neurological outcome after cardiac arrest. The PLR arc and the sensory tracts both pass the brain stem with anatomical proximity (Fig. 9). The PLR functions via the optic nerve, the Edinger–Westphal nucleus, and the oculomotor nerve. The SEP travels from the peripheral nerve to the spinal cord, via the medial lemniscus of the brain stem and then to the contralateral somatosensory cortex. The brain stem is more resilient to hypoxia than the cortex; however, if the hypoxic insult is severe, the PLR might be affected. Our hypothesis is that a patient with an absent PLR will have an absent SSEP. If true, certain NPi thresholds can predict absent SSEP response and therefore, it might be superfluous in neurological prognostication of certain patients after cardiac arrest.

Design & patents: A prospective, non-interventional, observational cohort study with consecutive inclusion. Eligible patients are adult (>18-years old) with in- and OHCA of any cause. We will include patients who require prognostic evaluation (i.e., remains comatose >48 h after ROSC). Results from routine pupillometry and SSEP are collected. Patient outcome will be assessed according to the mRS at the end of observation (hospital discharge). In total, 50 patients with a complete protocol will be included.

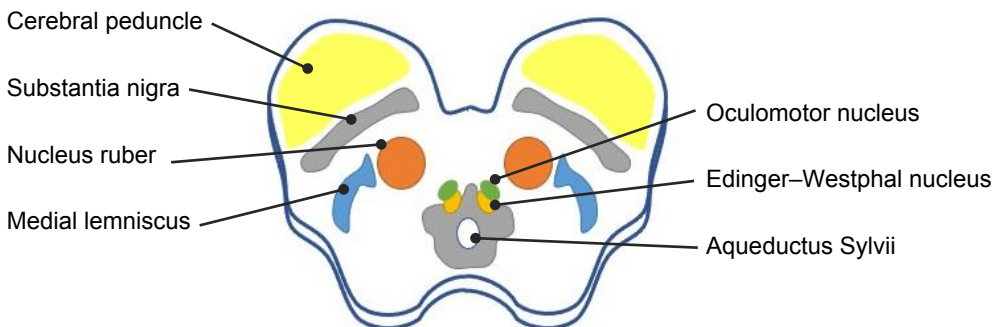


Figure 9. A schematic of the midbrain at the level of the oculomotor (III) nucleus.

4.6 STATISTICAL METHODS

The statistical analyses, with a few exceptions, were performed by the author, with guidance from colleagues, tutors, and the statistical consultant assigned to the project. Licenced versions of SPSS, Microsoft Excel, Microsoft Word, and SAS software were used. A p -value < 0.05 was considered significant in all statistical models. Tables were generated in Microsoft Word, and graphs were generated in Microsoft Excel or SPSS.

Descriptive statistics were used to display the mean and standard deviation or the median, interquartile range, or range, as appropriate. For paper **I**, Student's t -test was used to compare groups for continuous variables such as sedation doses. Fisher's exact test was used for categorical data such as temperature target group (34°C vs. 36°C). Multivariate logistic regression was used to determine the outcome influencing variables ($p < 0.2$) based on baseline characteristic differences. The probability of survival was displayed in a graph based on available data.

For paper **II**, the sensitivity, specificity, and confidence intervals were calculated both manually and via exact formulas in SAS. Cohen's kappa was used to assess interrater agreement with three raters used in the pair-wise comparison. Patient outcome was measured at ICU and hospital discharge. Sensitivity and specificity are described in Figure 10.

Paper **III** was a survey study, where descriptive statistics were used to display the results. McNemar's test was used to compare each clinician's prognostic assessment using the plain-text EEG reports versus the short, standardized statement.

For paper **IV**, the study size was calculated using the available values for NP_i and the prevalence of absent SSEP signal in the literature. Available NP_i values were medians and ranges, and the mean and standard deviation were calculated based on these values. Study size was estimated at 45 patients in order to detect a NP_i mean difference between groups of 0.7 with 0.01 significance. Because of the inherent uncertainty of these calculations, 50 patients with a complete protocol will be included in the study.

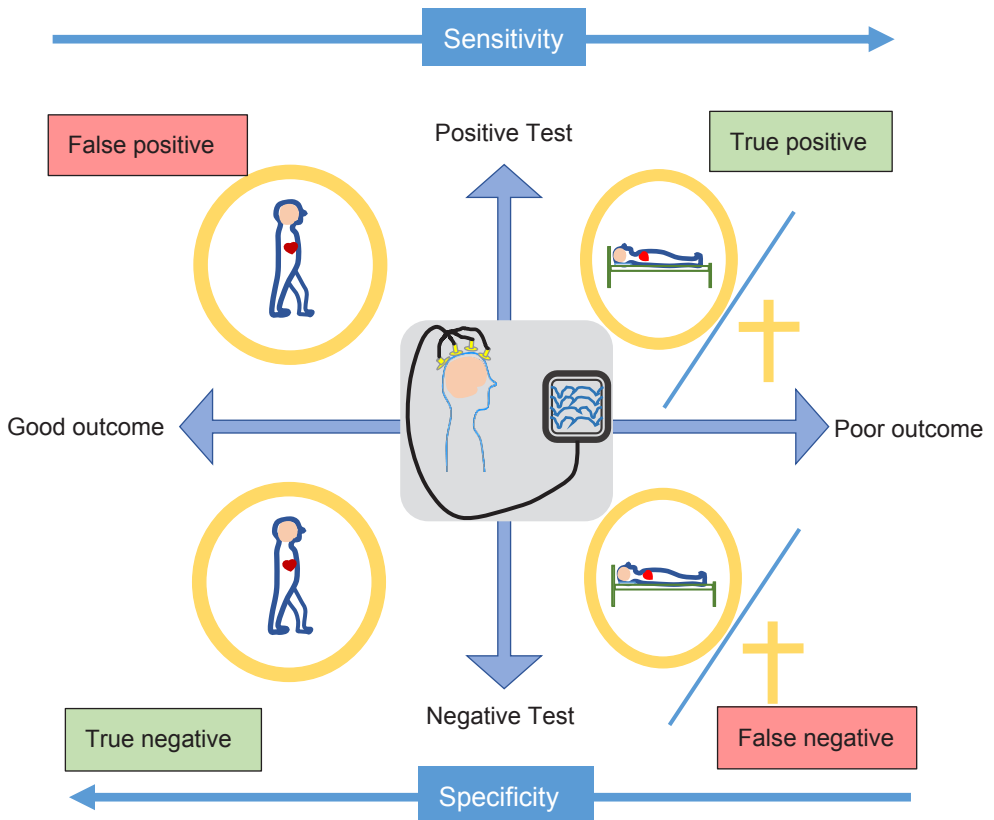


Figure 10. Schematic of a prognostic test (e.g., EEG) and the relationship to patient outcome in terms of sensitivity and specificity.

Sensitivity describes the ability of a test to reach an accurate (positive) result in patients with disease. A positive test in a disease-free patient represents a false positive. Sensitivity is calculated by dividing all of the true positive tests by the number of patients with disease (i.e., true positives divided by true positives and false negatives).

Specificity describes the ability of a test to reach an accurate (negative) result in disease-free patients. A negative test in a patient with disease represents a false negative. Specificity is calculated dividing all true negative tests by the number of disease-free patients (i.e., true negatives divided by true negatives and false positives).

5 RESULTS

5.1 PAPER I

A total of 197 patients were screened, and 79 were included in the final analysis: 38 from 2010 and 41 from 2014. Baseline characteristics differed, with more witnessed arrests in 2010 and a higher proportion of angiography performed in 2014. The 36°C group spent more time at the target temperature (83% vs. 75%; defined as targeted temperature + a maximum of 0.5°C).

Time to regain of consciousness was generally within five days of the cardiac arrest. Eight patients regained consciousness at >72h, and five of these “late awakeners” showed a good neurological outcome (Fig. 11). The sedation regime was similar with regard to total dose of propofol, fentanyl and midazolam administered during day two of intensive care.

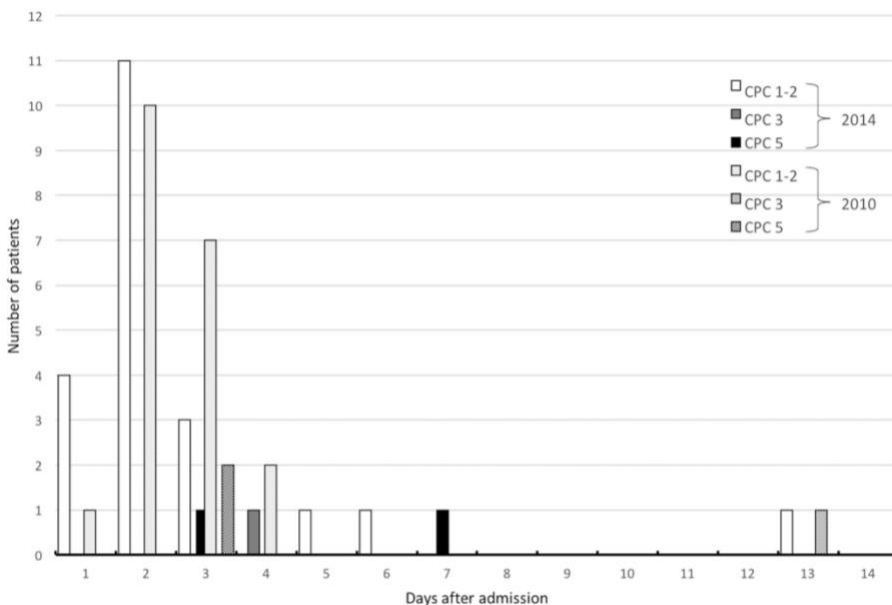


Figure 11. Time of regain of consciousness and CPC at hospital discharge for patients surviving hospitalization.

The X-axis indicates the number of days after cardiac arrest before the patient regained clinical consciousness. The pattern of the filled bars indicates the CPC status of the patient at hospital discharge. Patients remaining in the CPC 4 category were by definition comatose and, therefore, not represented in this figure. No patients with CPC 4 as their best CPC status survived to hospital discharge.

The mortality rate was comparable (42% vs. 44%), as were the neurological outcomes at all time points (Table 4). The median hospital length of stay was six days in patients with poor outcome and 15.5 days in patients with good outcome. The length of stay did not differ between the TTM groups.

Table 4. Neurological outcome at ICU discharge, hospital discharge, and 12 months after cardiac arrest.

	2010 (n=38)	2014 (n=41)	p-value
CPC at ICU discharge, no. (%)			
1–2	19 (50)	19 (46)	1.00
3–4	13 (34)	14 (34)	
Data missing	0	0	
CPC at hospital discharge, no. (%)			
1–2	20 (53)	19 (46)	1.00
3–4	1 (3)	2 (5)	
Data missing	1	2	
CPC at 12 months, no. (%)			
1–2	19 (50)	19 (46)	1.00
3–4	1 (3)	1 (2)	
Data missing	2	3	

5.2 PAPER II

A total of 62 patients were included in the final analysis, median age was 63.5 years and 77% of patients were male. Hypertension was the most common comorbidity (47%). Mortality was high (79%) and a poor outcome most common at hospital discharge (84%).

In six cases, the EEG was performed early (<24 h from ROSC) motivated by clinically suspected or overt seizures. In 39 of 62 cases, the EEG was performed >48h after cardiac arrest. The median (interquartile range) time from ROSC to EEG was 59 h (42–91 h).

The interrater agreement varied between substantial and fair (Table 5).

Table 5. Agreement between different pairs of raters.

		Senior consultant 1			
Senior consultant 2	EEG pattern category	“Highly malignant”	“Malignant”	“Benign”	Kappa
	“Highly malignant”	4	7	0	0.29
	“Malignant”	8	32	4	
	“Benign”	0	2	5	
		Senior consultant 1			
Resident	EEG pattern category	“Highly malignant”	“Malignant”	“Benign”	Kappa
	“Highly malignant”	7	2	0	0.62
	“Malignant”	5	35	1	
	“Benign”	0	4	8	
		Resident			
Senior consultant 2	EEG pattern category	“Highly malignant”	“Malignant”	“Benign”	Kappa
	“Highly malignant”	3	8	0	0.30
	“Malignant”	6	32	6	
	“Benign”	0	1	6	

Interrater agreement among three raters with Cohen’s kappa for each pair. The raters reviewed 62 EEG registrations independently and were blinded to clinical data and patient outcome. EEG patterns were classified into one of the standardized pattern categories: “highly malignant”, “malignant” or “benign”.

A “highly malignant” EEG pattern was found to be the most pessimistic pattern by any rater in 21 cases. The sensitivity and specificity of “highly malignant” patterns for poor outcome was 42% and 100%, respectively. In three cases the raters were in total agreement.

A “malignant” pattern was the most pessimistic pattern in 36 cases and the sensitivity and specificity for poor outcome was 54% and 25%, respectively. In total, 27% of all patients with a “malignant” pattern survived. In 28 cases the raters were in total agreement.

In four patients, all raters considered the EEG to be “benign”, i.e., absent of all highly malignant and malignant features. In these patients, three survived with good outcome and one died.

5.3 PAPER III

Of the 57 ICU clinicians who participated in the survey, 36 were specialists. The distribution of prognosis assessment is summarized in table 6.

EEG reports consistent with a “highly malignant” pattern were correctly assigned “poor prognosis” by 61% of clinicians from the plain-text EEG reports. By contrast, 93% correctly identified “poor prognosis” from the short statement confirming the presence of a “highly malignant” EEG pattern.

EEG reports consistent with a “malignant” pattern were assigned “poor prognosis” by 60% of clinicians from both plain-text and short statement reports. The proportion of correct prognostic assessments “prognosis not affected”, was 28% from plain-text reports and 40% from the short statement.

EEG reports consistent with a “benign” pattern were correctly assigned “good prognosis” by 64% of clinicians from plain-text reports and by 93% from the short statement.

Table 6. Prognosis assessment by 57 ICU clinicians.

EEG pattern category	Highly malignant		Malignant ¹		Benign	
	Plain-text reports (n=5)	Short statement	Plain-text reports (n=8)	Short statement	Plain-text reports (n=4)	Short statement
Poor prognosis	208 (73)	53 (93)	273 (60)	34 (60)	11 (5)	0
Prognosis not affected	65 (23)	4 (7)	128 (28)	23 (40)	70 (31)	4 (7)
Good prognosis	12 (4)	0	54 (12)	0	147 (64)	53 (93)

Data represent the number (%) of all answers per category. Summary of the alternatives chosen by 57 ICU clinicians (36 specialist and 21 residents) when asked to assess the neurological prognosis from plain text neurophysiologist EEG reports consistent with specific EEG patterns and short statements confirming the presence of a specific EEG pattern category.

¹ One answer from one specialist was missing.

5.4 PAPER IV

PLR and SSEP are both reliable predictors of poor neurological outcome after cardiac arrest. A severe hypoxic brain injury will affect the brain stem. The cortical SSEP response is likely to cease prior to the PLR due to the susceptibility of the cortex to hypoxic injury, a patient with absent PLR will likely have absent cortical SSEP response. We hypothesized that there should be a systematic relationship between PLR and SSEP.

Use of a pupillometer enables quantitative measurement of PLR, including the NP_i. NP_i can range from 0 to 5 which translates to a pupil reaction varying from absent to abnormally slow to normal.

The anatomical structures of the PLR arc and the sensory tracts are adjacent in the midbrain and both rely on intact brainstem function. Therefore, a severe hypoxic injury will inevitably affect both the PLR and SSEP. Theoretically, the PLR will first be abnormally slowed and then discontinued, corresponding to decreased NP_i values.

Our hypothesis is that a certain NP_i threshold will be predictive of an absent cortical SSEP response. If true, resource intensive SSEP could be excluded in certain patients and replaced with the easily operated pupillometer as a proxy in the multimodal prognostication after cardiac arrest.

6 DISCUSSION

This thesis investigated different aspects of neurological prognostication after cardiac arrest. We evaluated a targeted temperature change, different EEG report types and the performance of standardized EEG outside of the rigorous clinical trial protocols where they were first studied. Although the sample sizes of the cohorts were relatively small, the studies were designed for good external validity in order to provide important insights from the daily clinical practice.

The main findings were that TTM at either 34°C or 36°C could be used with sustained patient outcomes (**I**). Additionally, “highly malignant” EEG patterns were specific for poor neurological outcome in a routine practice cohort, although the interrater agreement varied from fair to substantial (**II**). Moreover, ICU clinicians identified correct prognosis to a higher degree from short, standardized statements as compared to descriptive plain-text reports (**III**). Furthermore, the identification of a systematic interrelation between NP_i and SSEP might enable exclusion of SSEP testing in certain patients in the multimodal prognostication after cardiac arrest (**IV**).

6.1 METHODOLOGICAL CONSIDERATIONS

This thesis comprised retrospective observational studies (**I–III**) and a study protocol (**IV**). Retrospective observational studies have several advantages including their simplicity of performance, cost-effectiveness, the ease and rapidity of data collection, and the ability to include longer time periods. The disadvantages include poor data quality, potential bias of variation by practice over time, and the fact that observations seldom yield firm cause-and-effect-grade evidence.

Because we aimed to study how TTM (**I**) and EEG (**II** and **III**) performed in clinical routines, we deemed the retrospective approach necessary. This enabled our easy data collection from two cohorts in order to compare the TTM targets (**I**). Had we instead collected the data prospectively, data acquisition would have taken multiple years, and the disadvantages of an observational study would still apply.

In paper **II**, three clinical neurophysiologists reviewed pruned EEG recordings due to a previous limitation in the storage capacity of the EEG database. Although, these versions accurately represented the overall recordings, it is possible that they might have negatively influenced our findings. However, in

a setting of varying interrater agreement, pruned EEG recordings and high levels of artefacts, “highly malignant” EEGs remained specific for poor neurological outcome. EEGs registered from 10 h, up to seven days after ROSC were included to allow detection of early and late EEG signs associated with good and poor prognoses (95). Because we aimed to study the clinical routine, we also included EEG data recorded outside of the timeframe recommended by the guidelines. Although, the early EEGs (<24 h) containing “highly malignant” features should probably not be named “highly malignant EEG”, given that the pattern categories were not developed within this timeframe.

We chose to only measure outcome at hospital discharge because we suspected that any false predictions of poor outcome would be detected at that time. We conducted neither a thorough neurological performance assessment nor a long-term follow up, although patients discharged with a neurological deficit may recover to a better neurological performance state after a couple of months. Neurological performance was scored based on available data using the CPC scale, which has been criticized for its resolution (20, 96); however, it was used here to allow comparison of our results with previous studies that applied the same scale. The currently recommended measurement for neurological outcomes is mRS which is included in the study protocol (IV) (97).

The survey (III) used ICU clinicians as the objects of investigation. This is an unusual but important perspective in clinical studies of patients subjected to critical clinical decisions. Although authentic EEG reports were used, the survey format necessitated some simplifications. Using a standardized patient case, we aimed to measure how each specific report affected which prognosis was applied by the clinicians. Two centres with both specialists and residents were used for better external validity. Nevertheless, our survey remains limited by language, local EEG reporting practice, and the clinicians that participated.

Additionally, in clinical practice, decisions concerning prognosis should be made by several clinicians following thorough discussion and multimodal testing. Our survey also lacked the ethical aspects of prognostication, as well as inclusion of information from the next-of-kin concerning the patient.

The NPi–SSEP protocol (IV) uses a prospective data collection. Because NPi and SSEP were introduced into routine practise in 2020 at our department, no retrospective data is available. Members of our research team will collect and register the data in the study database, and the mRS will be used to measure neurological outcome at hospital discharge, as recommended (97), to comply with uniform data reporting practice in order to facilitate study comparison.

6.2 PAPERS IN CONTEXT

6.2.1 PAPER I

In our study, the patients treated with TTM at either 34°C or 36°C showed similar outcomes, as neither mortality, nor neurological outcome differed at any timepoint. Our results should be regarded as an internal validation of a routine change, in accordance with the “TTM1 trial” (2).

The ICUs of the Sahlgrenska University Hospitals were among many ICUs that changed the temperature target after the “TTM1 trial”. A nation-wide study on ICU treated OHCA patients in Sweden reported a sudden drop in TTM use after the “TTM1 trial” was published. From 2010 to 2013, ~70% of patients received TTM at any temperature, whereas this percentage decreased to ~55% during the 2013–2015 time period. Although neurological performance and survival at 6 months did not differ between patients treated at 33°C and 36°C (98), the decreased use of TTM suggests lower adherence to guidelines and possibly worse outcomes for patients not receiving TTM. Moreover, the absence of difference in outcome reported in the “TTM1 trial” does not suggest that the TTM strategy should be abandoned.

In contrast to our results, a previous study reported worse results in patients treated at 36°C. Using a similar before-and-after method, they investigated changes in target temperature from 33°C to 36°C and reported a lower proportion of patients in active cooling, less time spent at the target temperature, and increased incidence of fever in the 36°C group (99). Although changes in outcome were not statistically significant, there was a possible trend toward worse outcomes.

Another group found similar hospital mortality but higher odds for favourable neurological outcome in patients treated at 33°C versus 36°C. Interestingly, the lower target temperature was initiated earlier, and the lowest temperature was maintained for a longer period of time relative to the higher temperature target (100).

Based on the results of the Swedish nationwide registry study and the two studies described here, one might think that the 36°C TTM protocol is considered as a less strict regime. If true, TTM 36°C could be inadequately applied and temperature target missed with possible worse patient outcomes as a result. Although the present study was small, the results implied that either 34°C or 36°C could be used with sustained patient outcomes if the protocol remains strict.

6.2.2 PAPER II

Our main findings were that “highly malignant” patterns showed high specificity for poor neurological outcome, and that the prognostic accuracy of the “malignant” patterns was poor. The interrater agreement varied between rater pairs, with a fair agreement between experienced EEG readers.

The good prognostic performance of “highly malignant” patterns has previously demonstrated in both “TTM1 trial” sub-studies and other studies including both TTM and non-TTM-treated patients (71, 72, 101-103). There are other EEG classification models than the standardized EEG pattern categories (Westhall model), such as the Hofmeijer model (104); however, when comparing the most pessimistic pattern categories of the Westhall and Hofmeijer pattern models (“highly malignant” and “unfavourable”, respectively) the Westhall model shows higher sensitivity (25% vs. 10%) (70).

The “malignant” pattern showed poor prognostic ability, in accordance with previous studies (71, 72). The term “malignant” is unfortunate in our opinion, given that it can induce a false sense of the prognosis. An alternative term, such as “indeterminate” proposed in the Hofmeijer model, would be preferable.

The interrater agreement varied even between experienced EEG readers in this study and was lower than that reported previously (94). Although, this might be expected at a centre not involved in the development of the standardized EEG categories. The low agreement between senior consultants suggests that specific training in standardized pattern classification would be useful, regardless of professional status.

The Westhall EEG classification model with the “highly malignant” pattern category is included in the ERC/ESICM draft guidelines (37). It is possible that the implementation could include significant interrater variability, as our results suggest. This might cause the identification of this specific negative prognostic factor to be delayed depending on the EEG reader.

6.2.3 PAPER III

In the survey, 93% of ICU clinicians correctly identified poor prognosis from the short statement “highly malignant EEG pattern present”. By contrast, 61% correctly identified the poor prognosis from plain-text EEG reports consistent with a “highly malignant” pattern. Additionally, the majority of ICU clinicians assessed the prognosis as poor when presented with the short statement “malignant EEG pattern present”.

The literature supports the use of “highly malignant” EEG patterns in neurological prognostication after cardiac arrest (70-72, 101). Moreover, the ERC/ESICM draft guidelines include “highly malignant” EEG patterns as a negative prognostic marker (37). According to the results from our survey, the presence of such a pattern must be clearly stated to avoid it being missed by the treating ICU clinician.

The “malignant” patterns are unreliably associated with poor outcome (71, 72). Additionally, a majority of the ICU clinicians incorrectly assessed the prognosis from the short statement “malignant EEG pattern present” as poor. We would therefore advise against the use of “malignant EEG patterns” in prognostication and the term “malignant” in EEG reports.

Patterns consistent with good prognosis could also be clearly stated in the report. The short statement “benign EEG pattern present” was interpreted as a good prognosis by 91% of ICU clinicians. We suggest that the EEG reader add a short statement, confirming the presence of a “highly malignant”, or “benign” EEG pattern to each EEG report consistent with such patterns.

6.2.4 PAPER IV

The proposed study (IV) will describe the relationship between NP_i values and the absence of SSEP cortical response. If the NP_i has the capacity to predict the absence of SSEP response, SSEP can be excluded in neurological prognostication of certain patients.

Similar studies have been conducted focusing on relationships between EEG and SSEP, with the results showing that SSEP is inevitably present in patients with a normal or “benign” EEG (74, 75). This suggests that SSEP is unnecessary in these patients. We reason that the same might hold true for absent NP_i and SSEP. If bedside NP_i can predict the absence of SSEP in certain patients, SSEP resources could be focused to patients for whom NP_i results are uncertain.

7 CONCLUSIONS

- I. Either 34°C or 36°C could be used as a targeted temperature in our department, with no detectable difference in mortality or neurological outcome between groups.
- II. A “highly malignant” EEG pattern is a strong predictor of poor prognosis, with no false positives identified in our study, although interrater agreement varied even between experienced EEG readers.
- III. Incorporating a short statement confirming the presence of “highly malignant” patterns in neurophysiologist EEG reports could improve their value for the ICU clinician assessing the neurological prognosis after cardiac arrest.
- IV. If NP_i can predict SSEP in certain patients, SSEP could be excluded in these patients to save resources. The proposed study will offer insight into the interrelationship between these two important prognostication methods.

8 FUTURE PERSPECTIVES

The effectiveness of hypothermic TTM remains debatable, and results of a large multicentre trial evaluating TTM 33°C versus strict fever control is expected soon (105). If hypothermia treatment proves superior, a return to cooling can be expected in centres that previously abandoned TTM after the first “TTM1 trial”. Otherwise, a debate concerning the importance of fever control will likely continue and additional prospective trials are necessary.

Regardless of TTM, prognostication remains a critical aspect of the post-resuscitation care in comatose cardiac arrest victims. Further studies are needed to evaluate the interrelationship of prognostic modalities in order to tailor the prognostication algorithm. Improved technical equipment might allow for simultaneous testing to further optimize the use of resources. Our research group will continue our investigations in the EEG, SSEP and NPi aspects of neurological prognostication after cardiac arrest.

Certain bedside tools for interpretation by the ICU clinicians can potentially improve patient care and prognostication. Examples include pupillometry rather than manual PLR assessment and EEG using a simplified montage to allow early identification of status epilepticus. The rapid implementation and availability of telemedical assessment during the COVID-19 pandemic might promote co-assessments between local and regional hospitals.

As indicated by recent studies on different biomarkers, their introduction into clinical practice can potentially improve overall prognostic accuracy, provided that the analysis methods are affordable (79-81). The most promising to date is determination of NFL, which is already provided by certain laboratories (80). However, the limitations remain the logistics required for sampling, transport, storage, and analysis.

In Sweden, we have several nationwide registries such as the ICU registry (www.icuregswe.org) and the CPR registry (shlr.registercentrum.se). The addition of a post-resuscitation registry might provide further insight into this important phase in the chain of survival. The interest in applying machine learning and artificial intelligence in medicine has increased in recent years; however, their application needs to be clinician driven with a focus on patient care in order to avoid misallocation of resources. In capable hands of individuals armed with adequate questions (and possibly powered by information from high quality registries), machine learning can potentially improve the post-cardiac arrest care.

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APPENDIX

The ICU clinicians received the following information at the time of the EEG survey:

You are in charge of conducting the neurological prognostication in a comatose survivor after cardiac arrest. It's day four after the cardiac arrest and the patient is intubated and on ventilator support. The patient has been evaluated with regards to myoclonus, reaction to pain, pupillary light reaction (PLR), corneal reflex, biomarker neuron specific enolase (NSE) and brain CT. In summary, the patient is not sedated, has no myoclonus, responds to pain with abnormal extension, has normal PLR and corneal reflex. The NSE biomarker is high, above reference for poor prognosis. Computerized tomography of the brain shows no distinct oedema.

The current recommendations suggest that in the current situation, the neurological prognosis can be assessed as poor if two prognostic tests, with accurate correlation to poor prognosis, are present. The patient above has one present factor, high NSE value, and you shall now evaluate how the neurophysiologist EEG report influences your perception of the patient's neurological prognosis.

Read each EEG statement separately, as if it belonged to the patient described, and evaluate its influence. State your answer by checking one of the boxes,

- The neurological prognosis is poor, because the EEG contains unfavourable patterns
- The neurological prognosis is not affected, because the EEG does not contain unfavourable or favourable patterns
- The neurological prognosis is good, because the EEG contains favourable patterns