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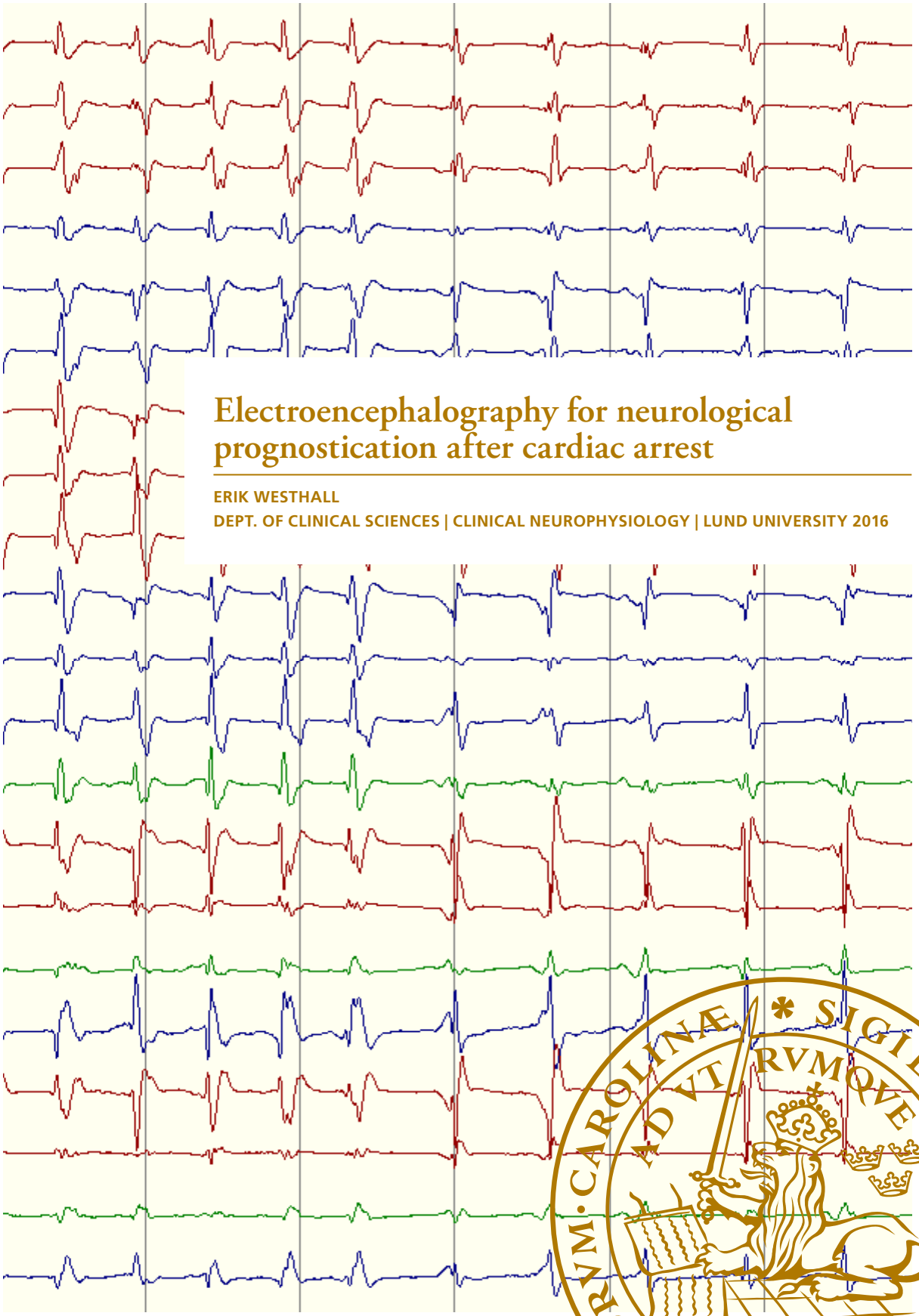
2016



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ERIK WESTHALL
DEPT. OF CLINICAL SCIENCES | CLINICAL NEUROPHYSIOLOGY | LUND UNIVERSITY 2016

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LUND
UNIVERSITY

DOCTORAL DISSERTATION
By due permission of the Faculty of Medicine, Lund University, Sweden.
To be defended at Segerfalk salen, Wallenberg Neurocentrum, Sölveg. 17, Lund
on Friday, March 18, 2016 at 09.00 a.m.

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Organization LUND UNIVERSITY Department of Clinical Sciences, Division of Clinical Neurophysiology	**Document name** DOCTORIAL DISSERTATION **Date of issue** March 18th, 2016
Author Erik Westhall	Sponsoring organization

Title Electroencephalography for neurological prognostication after cardiac arrest

Abstract

This thesis focuses on the prognostic value of electroencephalography (EEG) in comatose patients resuscitated after cardiac arrest (CA), using both simplified continuous EEG monitoring (cEEG) and routine EEG.

Background: Comatose survivors are admitted to an intensive care unit (ICU) to support vital functions. Post-resuscitation care includes target temperature management (TTM) for 24 hours. The degree of brain injury after CA varies among patients. Withdrawal of life-sustaining therapy due to presumed extensive brain injury is the most common cause of death during the hospital stay. Multiple prognostic tools are used to identify patients with a potential for recovery. Next to the neurological examination, EEG is the most commonly used tool to assess prognosis. However, the value of EEG has been limited by varying classification systems, interrater variability and influence of sedation.

Methods: In the “coma project” (2004-2008) consecutive patients at the general ICU in Lund were monitored with simplified cEEG from arrival until 120 hours after CA. Pre-defined cEEG patterns at different time points were correlated to outcome.

In the TTM trial (2010-2013) where patients were randomized to 33ºC versus 36ºC, a routine EEG was performed in patients still comatose after rewarming. The EEGs were classified into highly malignant, malignant and benign patterns by four EEG specialists from different countries according to the standardized EEG terminology proposed by the American Clinical Neurophysiology Society. The rationale and study design for this EEG evaluation was published.

Results: 95 patients in the “coma project” were monitored with simplified cEEG. A continuous background at start of registration or at normothermia strongly predicted a good outcome. All patients with electrographic status epilepticus (ESE) evolving from a burst-suppression background died without regaining consciousness whereas ESE evolving late from an established continuous background was compatible with good outcome.

At 8 selected TTM trial sites, routine EEGs were recorded after rewarming in 103 comatose patients. A highly malignant EEG was identified with substantial interrater agreement and had a specificity of 100% to predict poor outcome for all four EEG specialists. Any malignant EEG feature was identified with moderate interrater agreement but had a low specificity to predict a poor outcome (48%). A benign EEG was found in 1% of the patients with a poor outcome.

Conclusions: Simplified cEEG provides early positive and negative prognostic information in comatose patients after cardiac arrest.

A highly malignant routine EEG after rewarming reliably predicted a poor outcome. An isolated malignant routine EEG feature was not a reliable predictor whereas a benign routine EEG was highly predictive of good outcome.

Key words EEG, Interrater variability, Brain injury, Cardiac arrest, Hypothermia, Prognosis, Outcome

Classification system and/or index terms (if any)

Supplementary bibliographical information | **Language** English

ISSN and key title 1652-8220 | **ISBN** 978-91-7619-255-9

Recipient’s notes | Number of pages | Price

Security classification

Signature Erik Westhall Date 11/2 2016

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Cover photo by Erik Westhall, “Routine EEG with suppressed background and superimposed continuous generalized periodic discharges”.

Lund University
Faculty of Medicine
Doctoral Dissertation 2016:29

ISSN 1652-8220

ISBN 978-91-7619-255-9

Printed in Sweden by Media-Tryck, Lund University
Lund 2016

To Johanna

"When you change the way you look at things, the things you look at change."

-Max Planck

Contents

List of publications

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

I. Rundgren M*, **Westhall E***, Cronberg T, Rosén I, Friberg H. *Continuous amplitude–integrated electroencephalogram predicts outcome in hypothermia–treated cardiac arrest patients*. Crit Care Med. 2010:38(9):1838–44. *These authors contributed equally to the study.

II. **Westhall E**, Rosén I, Rossetti O A, van Rootselaar AF, Kjaer W K, Horn J, Ullén S, Friberg H, Nielsen N, Cronberg T. *Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management; rationale and study design*. BMC Neurology 2014, 14:159.

III. **Westhall E**, Rosén I, Rossetti O A, van Rootselaar AF, Kjaer W T, Friberg H, Horn J, Nielsen N, Ullén S, Cronberg T. *Interrater variability of EEG interpretation in comatose cardiac arrest patients*. Clinical Neurophysiology 2015, Dec;126(12):2397-404.

IV. **Westhall E**, Rossetti A O, van Rootselaar AF, Wesenberg Kjaer T, Horn J, Ullén S, Friberg H, Nielsen N, Rosén I, Åneman A, Erlinge D, Gasche Y, Hassager C, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T, Stammet P, Wanscher M, Wetterslev J, Wise M P, Cronberg T and the TTM-trial investigators. *Standardized EEG interpretation accurately predicts prognosis after cardiac arrest*. Published ahead of print in Neurology, Feb 10, 2016.

Abbreviations

aEEG	Amplitude integrated electroencephalography/gram
ACNS	American clinical neurophysiology society
BIS	Bispectral index
CA	Cardiac arrest
cEEG	Continuous electroencephalography monitoring
CI	Confidence intervals
CPC	Cerebral performance category scale
EEG	Electroencephalography/gram
ESE	Electrographic status epilepticus
GCS	Glasgow coma scale
ICU	Intensive care unit
IQR	Interquartile range
MRI	Magnetic resonance imaging
N20	Cortical peak in median nerve somatosensory evoked potentials
NPV	Negative predictive value
PEA	Pulseless electrical activity
PPV	Positive predictive value
qEEG	Quantitative electroencephalography/gram
ROSC	Return of spontaneous circulation
SIRPIDs	Stimulus-induced rhythmic, periodic, or ictal discharges
SSEP	Somatosensory evoked potentials
SW	Polyspike-/spike-/sharp-and-wave
VF	Ventricular fibrillation
VT	Ventricular tachycardia
TTM	Target temperature management
WLST	Withdrawal of life-sustaining therapy

Background

Cardiac arrest

Epidemiology

Sudden cardiac arrest (CA) is a serious medical emergency and a common cause of death. Most CA occur in the community outside the hospital. In Sweden the yearly incidence of out-of-hospital CA is around 50 per 100.000 inhabitants[1], which is similar to the rest of the western world[2,3]. Overall survival rates have increased in many countries during the past few decades[4-6] and is currently 11% in Sweden[7].

Figure 1. Sudden cardiac arrest
Illustration by Bo Jönsson. With permission.

Types and causes

CA are categorised according to the location of arrest. The aetiologies and causes of mortality are different when comparing out-of-hospital and in-hospital CA[8,9].

Furthermore, CA are categorised depending on the presenting electrocardiographic rhythm into ventricular fibrillation (VF), non-perfusing ventricular tachycardia (VT), pulseless electrical activity (PEA) or asystole. The shockable rhythms (VF or VT) are associated with a better survival than the non-shockable rhythms (PEA or asystole)[10], 34% compared to 4% according to recent Swedish registry data[7].

A cardiac cause of the arrest is the most common[11], typically due to coronary heart disease[12]. Non-cardiac causes, for instance suffocation or lung disease, also occur[13]. In these latter groups the brain is first suffering from hypoxia before the CA and subsequent combined hypoxic-ischemic insult.

Chain-of-survival

The "chain of survival"[14] with early call for help, early cardiopulmonary resuscitation including chest compressions and defibrillation is important for the chance of receiving return of spontaneous circulation (ROSC). Reducing the duration from the arrest to ROSC is important for long term survival and neurological outcome[15-17]. After return of circulation the last step in the "chain of survival", the post resuscitation care ensues.

Around 25% of patients in whom cardiopulmonary resuscitation was initiated will reach the hospital alive[7]. Among these, approximately half will die during the hospital stay typically due to hypoxic-ischemic brain injury without restoration of consciousness[18]. On the other hand, the majority of survivors have no or only mild neurological long term disabilities[18].

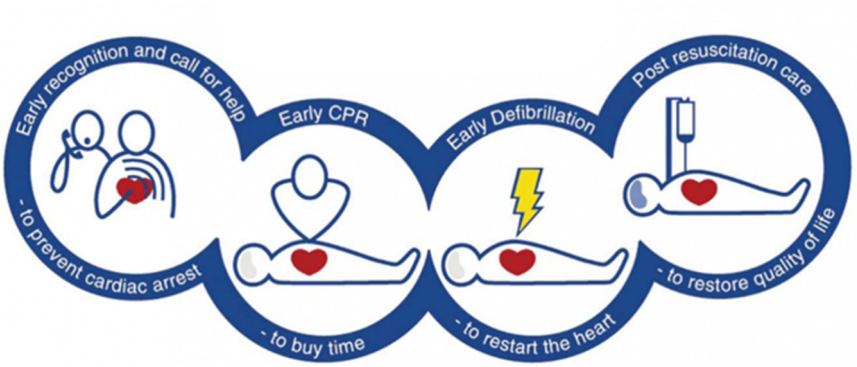

Figure 2. Chain of survival
Copyright European Resuscitation Council. Published with permission from the Swedish Cardiac Arrest Registry.

Experimental data of cerebral ischemia

The brain has a high metabolic demand mainly due to high energy consumption by neurons to maintain homeostasis and for signaling. The brain has nearly no capacity for energy production without a continuous supply of oxygen and nutrients.

Sudden CA leads to instant global ischemia. Animal studies have shown that the available energy compounds, for instance adenosine triphosphate (ATP), are immediately reduced and depleted within minutes[19,20] leading to neuronal damage[21,22]. The degree of brain injury is directly related to the duration of the ischemic insult.

The ischemic cell death occurs after a delay of hours to days after the insult. This delay may offer a window for therapeutic interventions[23]. The mechanisms leading to apoptotic or necrotic cell death are complex and involve cascades of deleterious events including loss of membrane potential, influx of calcium ions, glutamate release, damage to mitochondria, activation of destructive enzymes, free radical formation and toxicity due to nitric oxide production[24-30].

In experimental animal studies, induction of hypothermia during or after CA has been shown to ameliorate the hypoxic-ischemic brain injury[31,32].

Intensive care and target temperature management

Comatose survivors after CA are typically admitted to the intensive care unit (ICU) to support vital functions. Post-resuscitation care includes target temperature management (TTM).

In 2002 two randomized trials comparing TTM at 33°C for 12-24 hours with no active temperature control showed improved neurological outcome in the group treated with TTM[33,34]. In 2013 a large international trial showed no differences regarding mortality or neurological outcome comparing TTM at 33°C and 36°C for 24 hours[35].

In recent guidelines TTM is recommended for at least 24 hours with an option to choose a constant target temperature between 32°C and 36°C, but the exact target temperature is not specified[36].

The impact of the hypoxic-ischemic insult on multiple organ systems triggers a systemic inflammatory response syndrome, which is termed the post cardiac arrest syndrome. It includes brain injury, myocardial dysfunction and systemic ischemia-reperfusion response similar to sepsis[37,38].

The general management of these critically ill patients is complex and includes mechanical ventilation, sedation, circulatory support, coronary interventions, seizure management and more[37,39].

Brain injury and multimodal prognostication

Selective vulnerability

Specific brain regions and populations of neurons are more vulnerable to ischemia-reperfusion damage[40]. The cerebral cortex, hippocampus, cerebellum, thalamus and striatum are examples of such regions[41-43] whereas the brain stem is less affected[21].

Prognostication and withdrawal of care

The degree of brain injury after CA varies among patients. Withdrawal of life-sustaining therapy (WLST) due to presumed extensive brain injury is the most common cause of death during the hospital stay[18].

Most patients with extensive brain injury after CA will die days or sometimes weeks after the arrest without regaining consciousness. In some patients, however, there is a risk of persistent coma. The prevalence of patients in persistent coma varies significantly between countries and cultures and is dependent on what care is offered and what decisions are made with regards to life-sustaining therapies before leaving the ICU. The majority of patients remaining comatose at hospital discharge will stay in a persistent vegetative state despite neurorehabilitation, but sporadic patients with favorable recovery were reported[44].

A structured prognostication strategy to identify patients who have a chance to wake up and restore neurological function is very important. When a prediction of poor neurological prognosis is stated, a decision to withdraw intensive care is made in many countries (but not all). The requirements on such prognostic predictions must be high since a false prediction can lead to premature or erroneous WLST and death instead of a potential recovery[45]. A multimodal approach using multiple prognostic tools is therefore recommended[36,39,46].

Multimodal prognostic approach

When the comatose patient is admitted to the hospital some prognostic information can be obtained from the demographics and parameters of the arrest for instance, age, presenting electrocardiographic rhythm and time to restored circulation. However, these parameters and the initial clinical examination are often not reliable for definitive prognostication.

Brain stem and cortical functions may be totally absent early after CA in survivors with a good outcome and prolonged observation in the ICU is therefore needed. Primitive brain stem functions reappear first and at a later stage recovery of cortical functions and consciousness may occur[47].

Repeated clinical neurological examinations are the foundation for reliable prognostication and are based on assessment of coma depth including reaction to pain stimuli, testing of brain stem functions such as pupillary and corneal reflexes, and in addition observation of convulsions and spontaneous movements.

The prognostic ability of the clinical examination is dependent on the time after CA[36] and, unless the patient awakens, this examination is unreliable during the first days. Further, TTM requires sedation and sometimes neuromuscular blockade, which complicates prognostication. Therefore, additional prognostic tools such as neurophysiological methods, neuroimaging and biochemical markers

are recommended to support the clinical prognostication (figure 3). The neurophysiological methods commonly used for prognostication are electroencephalography (EEG) and median nerve somatosensory evoked potentials (SSEP).

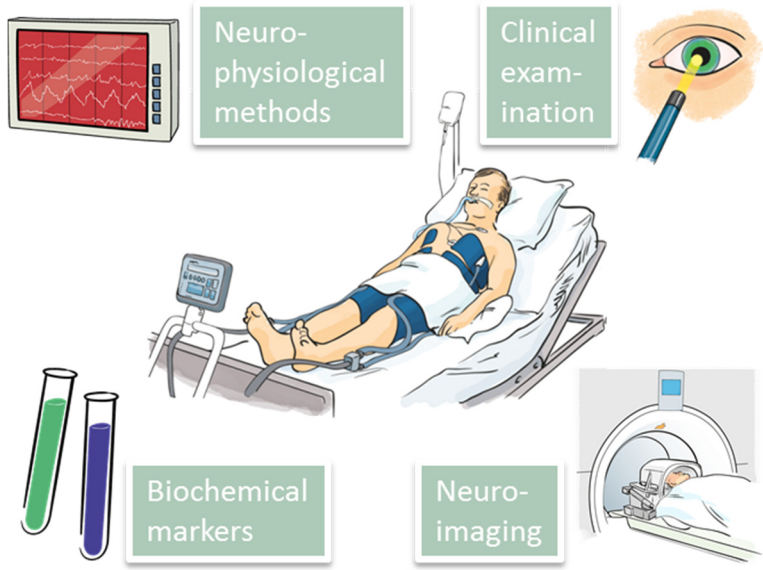

Figure 3. Multimodal prognostication
Illustration by Bo Jönsson. With permission.

Clinical convulsions

As a consequence of brain dysfunction clinical convulsions, regardless of EEG correlates, are common after CA and found in approximately one third of patients[35]. They can appear as clonic, tonic-clonic or most often as myoclonic seizures also termed myoclonus.

Myoclonus is a clinical phenomenon with sudden, involuntary, brief twitches that can be stimulus induced. A proposed definition for status myoclonus is continuous and generalized myoclonus for ≥30 minutes in comatose patients after CA[39]. This definition is clinically defined regardless of EEG pattern.

Clinical convulsions, especially status myoclonus, are associated with a poor prognosis[48-50].

EEG after cardiac arrest

History and physiology

The EEG signal was first discovered by the German psychiatrist Hans Berger nearly one hundred years ago (1925). In the 1930s the technique was rediscovered and brought into clinical use, primarily to investigate epileptic seizures.

The source of the EEG signal is the pyramidal cells in the brain cortex[51]. The small electrical signals from these neurons are summated in space and time so that the EEG activity can be recorded with surface electrodes on the scalp.

The cortical EEG activity is modulated and synchronized by subcortical "pacemaker neurons" in the thalamus. In addition to these thalamocortical circuits the EEG is also modulated by connections within the cortex and by neurons that regulate sleep wake cycling in the brainstem (reticular activating system). In other words, EEG allows immediate assessment of cortical and subcortical function.

Since the 1960s EEG recordings have been used to evaluate prognosis in comatose patients resuscitated after CA. Several classification and grading systems of EEG after CA have been proposed during the years and one of the first was published by Hockaday in 1965[52]. Numerous studies using routine EEG were published during the following years. Unfortunately many different classification systems were used for prognostication and for defining electrographic seizure activity, which has hampered the evidence for using EEG after CA[53-55].

There has been an increasing interest in EEG after the introduction of TTM following the initial randomized trials on induced hypothermia in 2002[33,34].

The intensive care management has also developed considerably during the past decades and there is an increasing need for monitoring of body functions and reliable prognostication to guide treatment decisions.

The increasing interest in EEG patterns in critically ill patients and the urgent need for a consensus on how to describe these patterns led to the development of a standardized EEG terminology for critically ill patients proposed by the American clinical neurophysiology society (ACNS) in 2005[56]. The revised version of this terminology published in 2013[57] also included a classification of background activity making it suitable for use after CA. Standardization of EEG interpretation is essential for reproducibility, meta-analyses and application of study results into clinical practice.

Figure 4 shows common EEG patterns after CA with some examples of definitions according to the ACNS EEG terminology.

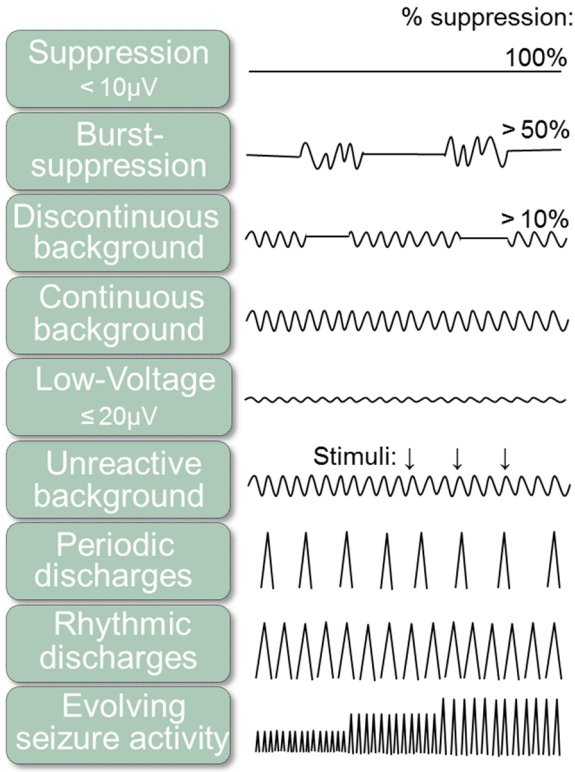

Figure 4. Common EEG features after cardiac arrest
Criteria for background voltage and suppression-ratio (proportion of recording that constitutes suppression periods) according to the ACNS EEG terminology.

EEG and cerebral ischemia

The cortical neurons are in constant need of blood supply for oxygen and nutrients to maintain signaling and integrity. The EEG is therefore very sensitive to hypoxia or ischemia. Initial changes in ischemia include slowing of the background frequencies and appearance of periods with extremely low-voltage EEG, termed suppression periods. If the cerebral blood flow decrease below approximately 10mL per 100g brain tissue per minute all EEG background is suppressed and brain injury starts to develop[58]. The degree of brain injury depends on the duration of time with low or no blood flow. After restored circulation the electrophysiological recovery of cortical activity or failure of recovery can be monitored with EEG.

Experimental animal models

The electrophysiological changes after CA have been studied in several animal models using EEG monitoring[59-70]. Within a few seconds to half a minute after CA the EEG was totally suppressed. Electrophysiological recovery was monitored over the following minutes to hours. After an initial period of complete suppression an alternating pattern, with bursts of cortical activity alternating with periods of suppression, was seen before the alternating pattern merged to a continuously appearing cortical activity. The duration of suppressed EEG and latency of appearance of a continuous background was correlated to neurological outcome as well as neuropathological injury.

Human data and natural course of recovery

Case reports of patients that underwent EEG monitoring in the operating room during a circulatory arrest provide some insights to the electrophysiological changes directly after a sudden CA in humans. Within approximately ten seconds there is a generalized suppression of all EEG activity. Cortical activity returned within minutes after restored circulation but the duration of these circulatory arrests were shorter compared to a typical out-of-hospital CA[71,72].

Important work in describing the evolution of EEG in patients resuscitated after sudden CA was performed by Jørgensen and colleagues in the 1980s using repeated prolonged EEG recordings[73,74]. They proposed a sequential recovery of cortical activity with three phases. At first the EEG was suppressed with no detectable cortical activity followed by a discontinuous intermittent cortical activity followed by a continuously appearing cortical activity.

Patients not receiving TTM (n=125) who had a suppressed EEG when the monitoring was initiated, soon after restored circulation, were included in Jørgensen's initial studies. All the patients that later regained consciousness (n=37) restored a continuous background within the first day[73]. The cortical activity was first seen in the frontal leads and appeared discontinuously with alternating periods of suppression before merging into a continuous cortical activity with amplitudes above 20μV[47]. The amplitudes and frequencies of the continuous background improved further with time. The time to return of a continuous background correlated exponentially with the time point when the patients regained consciousness[75]. On the contrary, in the patients that remained unconscious until death (n=88) the electrophysiological recovery was often incomplete or delayed[74]. Only half (n=44) of these patients with poor outcome restored a continuous background within 1-5 days. A minority (n=17) restored no cortical activity and had a suppressed EEG until death and some (n=27) restored a discontinuous cortical activity but never a continuous background.

EEG and target temperature management

Ongoing controlled temperature down to the level of 32°C does not *per se* significantly affect the EEG in humans[76,77]. However, the EEG activity is sensitive to sedation[78], which is used during TTM. In sufficient doses sedation can cause burst-suppression and in very high doses even a totally suppressed EEG[79]. During mild hypothermia, clearance of drugs is prolonged with the risk of residual effects of sedation after stopping infusion of the drugs. The use of short acting sedatives has been suggested[36]. To what degree sedation in clinically used doses during TTM affects the EEG is not fully known. EEG interpretation can also be complicated by artefacts that accompany TTM, for instance from muscle shivering, mechanical ventilation or electrical equipment in the ICU environment.

In summary, the temperature levels used during TTM do not seem to affect the EEG whereas sedation and artefacts that accompany TTM may affect reliability.

Routine EEG methodology

Routine EEG is a standard procedure used around the world. It is non-invasive, safe, inexpensive and available within a few hours at most hospitals, at least during office hours. Multiple electrodes, usually 16-21 surface electrodes, are positioned over the scalp according to the international 10-20 system and the typical duration of recording is 20-30 minutes. It is performed by trained EEG technicians and allows testing for reactivity to external stimuli. In the digital systems used nowadays simultaneous video recording of the patient is easily performed, which facilitates interpretation and correlation to clinical convulsions. In comatose patients with artificial ventilation, muscle relaxants are often useful to reduce artefacts from muscle and movements.

cEEG methodology

Continuous EEG monitoring (cEEG) is increasingly used in the ICU to evaluate diverse motor phenomena and detect electrographic seizures and changes in background activity, which may have therapeutic implications[80].

Performing a multichannel cEEG over several days is relatively expensive and resource consuming regarding manpower[81].

Frequent or continuous monitoring with EEG after CA is recommended in guidelines[82,83]. Treatment of clinical and electrographic seizures after CA is also recommended[36], but whether cEEG monitoring, routine EEG or even no EEG should be used in the diagnosis and treatment remains controversial due to resource utilization and lack of evidence for improving outcome[36,81].

Simplified cEEG methodology

It is often challenging to provide "gold standard" multichannel cEEG monitoring around the clock outside the large centres, since it necessitates EEG technicians and regular review by EEG specialists. Therefore, methods to simplify recordings and interpretations have been developed in recent years[84].

Montages

Simplified montages, which can be applied by trained ICU nurses around the clock can be used to screen for seizures and monitor gross changes of the background activity[85].

Studies on adult patients with seizures using simplified montages with 4 to 7 channels report a somewhat lower sensitivity (68-93%) to detect seizures and a preserved specificity (94-98%) compared to a multichannel cEEG[86-89]. Such comparisons have not yet been performed in CA patients, who have a high proportion of generalized discharges, and therefore the detection rate in a simplified montage would likely be higher than in the mentioned studies.

qEEG trending

Techniques using quantitative EEG measurements (qEEG) can be applied to ease interpretation by displaying time compressed trends of qEEG data. Many of these tools also facilitate interpretation by giving numeric values or display simplified trends adapted for visual pattern recognition.

Amplitude integrated EEG (aEEG) is an example of such trend monitoring. The use of aEEG is well established for decades in the neonatal ICU, where it provides prognostic information after asphyxia and facilitates detection of subclinical seizures[90,91].

A recent study on adult patients with seizures of mixed etiologies found a sensitivity of 84% and a specificity of 69% to detect seizures using a panel with four qEEG trends, including aEEG, displaying simplified qEEG data from each hemisphere, with no access to the original EEG signal[92]. A combined interpretation of qEEG trends and the original EEG signal is recommended and enhance reliability of seizure detection and artefact recognition[91].

Examples of other modalities of qEEG that have been explored after CA are suppression-ratio (degree of discontinuity), bispectral index (BIS) and entropy measurements.

Automatic detections

Promising automated detections and alarms for events like electrographic seizures have been developed and further improvement of these qEEG techniques is ongoing.

Figure 5 summarizes some of the differences between a multichannel routine EEG and simplified cEEG monitoring.

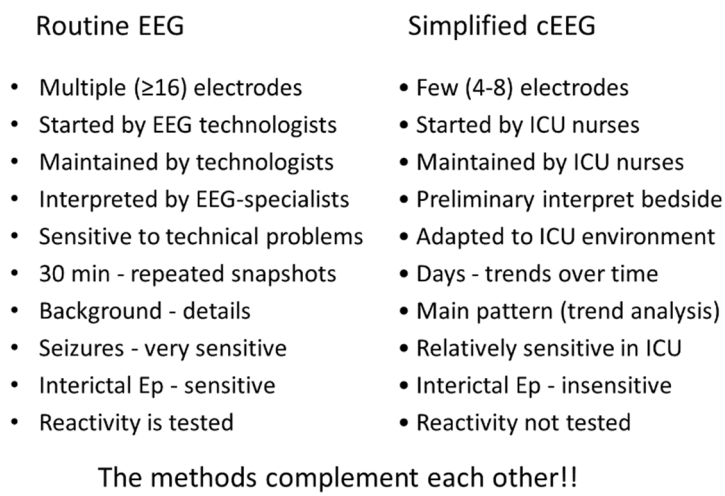

Figure 5.
Differences between a routine EEG and simplified continuous EEG monitoring.

Characteristics of an optimal prognostic test

Several statistical terms are used to describe the prognostic ability of a test. Sensitivity (true positive rate) measures the proportion of patients with poor outcome that are correctly identified by the test. Specificity (true negative rate) measures the proportion of patients with good outcome that are correctly identified. An optimal prognostic test should have both sensitivity and specificity of 100% or very near 100%. Prerequisites to obtain this are that the methodology is robust, and if the test result is dependent on an assessment the interrater variability among the assessors has to be low. The method should also be specific for the injury that it is supposed to assess and for which prognostication is based on. For instance, EEG can apart from the brain injury also be reversibly affected by sedation and metabolic factors.

To describe the reliability of a test to predict poor outcome the most important factor is the false positive rate (FPR)[93]. For instance, a test with an FPR of 15% would mean that in 15% of the patients with a good outcome the test results would instead falsely have predicted a poor outcome, with an inherent risk of premature WLST. This explains why the FPR has to be as low as possible, with narrow 95% confidence interval (CI), if the test is to be used for prediction of outcome.

When investigating the prognostic ability of a test the results should optimally be blinded to the treating team, otherwise there is a risk that the findings directly or indirectly affect level of care and decisions on WLST. The risk of a so called self-fulfilling prophecy is present in a majority of prognostic studies after CA and may lead to the reporting of a falsely high specificity for a test to predict poor outcome[54,55].

EEG for prognostication

Meta-analyses and the level of evidence for prognostication using EEG have been hampered mainly by the inconsistent use of classification systems and definitions between studies. Also variations regarding the time points of EEG recording complicate meta-analyses, since the EEG patterns are not stable but rather evolve during the first days after CA. Thereby the prognostic value of a certain EEG pattern can change considerably depending on the time point after CA. Other important limitations of EEG are influence of sedation, interrater variability and varying methodological setups, for instance electrode montages. Due to the diversity of used definitions, some described patterns are only evaluated in a few studies risking so called publication bias[94]. Several reviews and meta-analyses of the literature have been performed[53,95-97] and complemented with evidence from recent years including patients that have received TTM or were monitored with cEEG[54,55,94]. Most studies included in these reviews lack blinding of the treating team to the EEG results and criteria for withdrawal of care is often not described and therefore the risk of self-fulfilling prophecy cannot be excluded.

This topical summary of the prognostic value of EEG in adults is primarily based on these reviews, with the addition of some case reports and recent publications. No systematic search criteria of the literature was applied. The focus is primarily on malignant patterns such as suppression, burst-suppression, unreactive EEG and abundant epileptiform activity. The prognostic values are reported separately for TTM-treated and non-TTM-treated patients, mainly due to the risk of lingering sedation after TTM but also since studies using TTM were performed during the recent years and these patients received modern intensive care.

Routine EEG prognostication

Routine EEG has been a standard examination and recommended for prognostication after CA for many decades and it is still the most common tool used in addition to the clinical neurological examination[98].

The recent standardized ACNS EEG terminology has previously not been explored prospectively in routine EEG studies after CA. Most previous studies cannot be retrospectively classified according to this terminology and therefore, when performing meta-analyses, the existing evidence is often lumped together in wider categories with inconsistent definitions.

Unfavourable EEG

Non-TTM-treated patients

A meta-analysis by Wijdicks 2006 included five studies with 223 non-TTM-treated patients. The patients with "unfavourable EEG patterns" were lumped together (suppression, burst-suppression, alpha-theta-coma, generalized periodic complexes) and had an FPR of 3% (95%CI 1-11) for predicting a poor outcome (≈CPC3-5 at 1-6 months)[53]. The authors also proposed a subgroup of malignant patterns and concluded that "generalized suppression, burst-suppression with generalized epileptiform activity, or generalized periodic complexes on a flat background are strongly but not invariably associated with outcomes no better than persistent vegetative state".

TTM-treated patients

In a recent meta-analysis by Golan 2014 including 11 studies with 552 TTM-treated patients an "unfavourable EEG pattern" (suppression, burst-suppression, unreactive pattern, status epilepticus) had an FPR of 7% (95%CI 4-12) for predicting a poor outcome (CPC3-5 at hospital discharge-6 months)[94]. The timing of EEG recording was within 72 hours after ROSC in eight studies and beyond 72 hours in three studies. It is noteworthy that FPR was 4% (95%CI 1-8) before 72 hours and 0% (95%CI 0-3) after 72 hours. In the conclusion the authors suggested delaying prognostic testing to beyond 72 hours after ROSC.

Suppressed or low-voltage background

The description of an EEG background with low amplitude differs between studies regarding both chosen nomenclature and amplitude thresholds.

The terms electrocerebral inactivity or isoelectric EEG were used historically mainly in the context of brain death evaluations and were defined as "no activity >2μV" in a recording fulfilling certain rigid technical standards[79]. These terms are omitted in the recent ACNS terminology.

In the ACNS terminology the term suppression is defined in a longitudinal bipolar montage as "all activity <10μV during the entirety of the recording" and a low voltage background as "most or all activity <20μV" whereas background amplitudes >20μV is classified as normal[57].

Most previous EEG studies used a higher amplitude threshold in their definition of suppression compared to the ACNS terminology and thus included low voltage EEGs in the term suppression. A low voltage background in a comatose CA patient is still considered a grossly abnormal sign and should not be confused with a low voltage EEG without focal or generalized slowing that can be found as a normal variant in awake healthy persons, which may be explained by a lesser degree of synchronization in those individuals[79].

Historically an isoelectric, suppressed or low voltage background was considered a highly malignant sign if persistent >24 hours after CA in a normothermic patient unaffected by sedatives or metabolic disorders. This is in concordance with the studies of Jørgensen where failure of recovery from the initial most malignant phase after CA with no cortical activity lead to poor outcome in all patients[74].

Non-TTM-treated patients

If patterns with background amplitude <20μV are lumped together 11 routine EEG studies with non-TTM-treated patients were found[52,99-108]. All EEGs were performed >24 hours after CA. None of these studies reported any false positives.

The exact number of patients with suppression in most of these studies are unknown since grading scales were used and therefore sensitivity and confidence intervals cannot be calculated.

Using routine EEG, only one surviving non-TTM-treated patient with background amplitudes between 10 and 20μV beyond 24 hours after ROSC that recovered consciousness has been reported[96].

TTM-treated patients

Six small routine EEG studies that used TTM on most patients were found[109-114]. In total 163 TTM-treated and 57 non-TTM-treated patients were included and the presence of low amplitude EEGs were reported, but in neither of these studies was the evaluation of routine EEG background the primary purpose of research. Five of these studies reported in total 54 patients with low voltage or isoelectric EEGs and all had a poor outcome[109,110,112-114]. The sixth study reported 10 patients with low amplitude EEGs of whom one patient had a good outcome (CPC1-2) but whether the amplitudes were <10μV or between 10 and 20μV was not reported[111].

In addition, one large routine EEG study based on reviews of EEG-reports with the aim of retrospectively classifying the EEGs according to the recent ACNS terminology included 166 TTM-treated and 53 non-TTM-treated patients and reported 26 patients with suppressed background and all had a poor outcome[115].

Low-voltage EEG in TTM-treated patients was also explored using cEEG monitoring (see separate section below).

Summary (suppressed or low-voltage routine EEG)

To our knowledge there has been no patients, TTM-treated or not, surviving with good outcome with generalized suppression below 10μV in a full-lead (>16 channels) normothermic recording of good quality at a time point beyond 24 hours after CA and free of significant metabolic or pharmacological influence.

However, it is important to observe that there are survivors with a suppressed EEG during the first 24 hours after CA or when simplified electrode-montages were used even after that time point, which is further described in the section on cEEG monitoring below.

In addition to anoxic-ischemic injury the EEG amplitudes may be affected by sedation, technical factors and individual patient factors[39]. In recent guidelines it was suggested against using low-voltage EEG for prognostication due to this possibility of interference[36].

Interpretation of a low-voltage EEG can also be especially complicated by artefacts, and the use of muscle relaxants in mechanically ventilated comatose patients is often helpful.

Additional studies using routine EEG, especially in TTM-treated patients, are needed to establish if a suppressed background according to the ACNS terminology reliably predict a poor outcome.

Burst-suppression or discontinuous background

The second phase of electrophysiological recovery according to Jørgensen is a discontinuous intermittent cortical activity with bursts of cortical activity alternating with periods of suppression[73].

The ACNS terminology states that in burst-suppression the suppression periods must constitute >50% of the recording. If suppression periods constitute 10-49% the definition of discontinuous background is fulfilled and if they constitute <10% the term nearly continuous background should be used.

The definitions of burst-suppression vary considerably between studies both regarding burst criteria and suppression criteria. The most liberal definitions of burst-suppression include patterns with occasional periods of suppression with duration of one second without any criteria for the bursts. Such a pattern could even be classified as a nearly continuous background according to the ACNS terminology.

Non-TTM-treated patients

When considering all studies in which the authors claimed to encounter burst-suppression, 13 routine EEG studies on non-TTM-treated patients were found[100-102,104,105,116-123]. One of these studies reported an FPR of 5% (95%CI 0-26) due to a single false positive patient with burst-suppression between 24 and 48 hours after CA who survived, but neurological function was not reported[105]. In another one of these studies two patients with burst-suppression between 24 and 72 hours had a good outcome (CPC 1-2 at 3 months) resulting in an FPR of 29% (95%CI 4-71)[116]. The remaining 11 studies reported no false positives[100-102,104,117-123].

An additional four routine EEG studies on non-TTM-treated patients were found, which did not use the term burst-suppression but instead reported backgrounds with suppression periods lasting >1 second[52,99,103,108]. Three studies[52,99,103] reported no false positives and the fourth study[108] reported two patients with full recovery after CA of non-cardiac cause (respiratory failure and barbiturate intoxication) but it was unclear when the EEGs were recorded.

TTM-treated patients

Eight routine EEG studies that used TTM on most patients were identified[109-115,124]. In six of these studies burst-suppression patterns were reported in 43 patients and all had a poor outcome[109-112,114,115]. The remaining two studies reported 22 patients with burst-suppression, of whom one patient had EEG reactivity to stimuli and recovered awareness[113] and one patient was likely affected by low dose fentanyl infusion during recording and had a good long-term outcome (CPC1-2)[124].

Another routine EEG study included 90 patients with a reactive background during ongoing TTM and reported 11 survivors (CPC1-3) among 20 patients with a discontinuous background during normothermic conditions up to 24 hours after rewarming[125]. Discontinuous background was defined as suppression periods constituting >10% of the recording in concordance with the ACNS terminology.

Summary (burst-suppression or discontinuous routine EEG)

Definitions of burst-suppression were not described or were inconsistent among studies.

No routine EEG studies concluded that burst-suppression could be used to predict poor prognosis during the first 24 hours after CA.

Both in non-TTM-treated and in TTM-treated patients a burst-suppression pattern beyond 24 hours after CA was strongly associated with a poor outcome. However, sporadic survivors with a good outcome and burst-suppression possibly even up to 72 hours after CA were reported, but the definitions used were unclear.

Burst-suppression in TTM-treated patients was also explored using cEEG monitoring (see separate section below).

Alpha-theta-coma pattern

The term alpha-theta-coma pattern has primarily been used in the early routine EEG studies before TTM was introduced. There is no definitive consensus on definitions. Definitions most often include an unreactive background with frequencies within the alpha or theta bands often with the highest amplitudes in the anterior leads (reversed anterior-posterior gradient).

Non-TTM-treated patients

A meta-analysis[36] of the presence of an alpha-theta-coma pattern during the first seven days after CA included six studies with non-TTM-treated patients[103,126-130]. Alpha-theta-coma pattern had a positive predictive value of 88% (95%CI 74-96) and could therefore not reliably predict a poor prognosis.

TTM-treated patients

In recent years two routine EEG studies included 75 TTM-treated and 31 non-TTM-treated patients and reported alpha-theta-coma. In the first study two non-TTM-treated patients had alpha-theta-coma of whom one survived[114]. In the second study one patient with alpha-theta-coma during ongoing TTM had a good outcome, but all patients with alpha-theta-coma after rewarming had a poor outcome[131].

Unreactive background

The prognostic value of EEG reactivity was first noted in the 1950s[132] and was later incorporated in EEG grading scales[118,133].

Non-TTM-treated patients

In studies of non-TTM-treated patients the prognostic value of reactivity *per se* is difficult to evaluate since reactivity was part of grading scales, and the number of patients with unreactive EEG was not separately reported.

TTM-treated patients

Absence of background reactivity to external stimuli in TTM-treated patients after rewarming was evaluated in nine studies[49,111,113,131,134-138], most of them used routine EEGs. In five of these studies all patients with absent reactivity had a poor outcome (CPC3-5) when testing was performed after rewarming[111,131,136-138]. However, when testing was performed during ongoing TTM four patients with absence of reactivity had a good outcome[131,137,138]. In the four remaining studies there were in total nine patients that restored awareness and at least seven of them had a good long-term outcome (CPC1-2) despite absence of reactivity after rewarming[49,113,134,135].

qEEG analysis

A recent study found only moderate interrater agreement for visual analysis of reactivity between three EEG specialists[139]. Quantification of reactivity using qEEG techniques have shown promising results[139,140], but need to be further validated.

cEEG prognostication

Continuous or serial EEG monitoring is likely to provide more reliable prognostic information compared to a single routine EEG[141], but this has not been proven. In addition, cEEG is used to identify potentially treatable conditions such as electrographic seizures.

When assessing the prognostic value of cEEG it is of profound importance to take the evolution of EEG during the first days after CA into account.

According to the hypothesis of Jørgensen, electrophysiological recovery starts with suppression, followed by a discontinuous background and thereafter a continuous background appears before the patient regains consciousness[73].

Background predictors of good outcome

The first cEEG study in TTM-treated patients by Rundgren and colleagues showed that an early debut of a continuous background during ongoing TTM is a strong predictor of a good outcome[85] and similar findings have been shown in several cEEG studies[131,134,137,142-146].

Another early predictor of good outcome is a reactive background to external stimuli. A prospective study of 34 patients found EEG reactivity during TTM in all 19 surviving patients and the majority of them had a good outcome (CPC1-2)[147].

Background predictors of poor outcome

Inconsistent definitions

Definitions of discontinuous, burst-suppression, low-voltage and suppression varied among the studies. Only two studies[134,148] reported EEG patterns according to the ACNS terminology.

Depending on the definitions used a low-voltage, suppressed, discontinuous or burst-suppression background during TTM was not invariably associated with a poor outcome. Instead, a large fraction of good outcome patients had these patterns, especially early during TTM[85,134,144,146,148,149].

Suppressed or low-voltage background

In two studies using strict definitions and multichannel cEEG monitoring, a low-voltage background (<20μV) 24 hours after CA during ongoing TTM and sedation had 100% specificity to predict a poor outcome[134,144], but these findings need to be validated in future studies.

In other studies using simplified montages a low-voltage or suppressed background was not invariably predictive of a poor outcome, even beyond 24 hours[146]. This can be explained by the inherent definition of the term generalized suppression, which states that the entire record consists of suppression in all channels using a multichannel montage. In conclusion, when encountering a low-voltage or suppressed background using a simplified montage, especially if the signal-noise-ratio is not optimal, confirmation of generalized suppression for reliable prognostication necessitates a multichannel EEG including testing of reactivity.

Burst-suppression or discontinuous background

Ten studies reported burst-suppression or discontinuous backgrounds during ongoing TTM, but with inconsistent definitions[85,131,134,137,142,144,146,148-150]. Six of these studies reported in total 36 survivors with burst-suppression at one point during TTM and a good outcome[131,137,142,144,146,150]. In the remaining four studies all patients with a burst-suppression at any time had a poor outcome[85,134,148,149]. The definitions of burst-suppression in the latter four studies were somewhat more conservative compared to the former six studies.

qEEG indices

Several simplified qEEG indices that were originally developed to assess depth of anaesthesia have been explored as prognostic tools after CA.

Six studies using bispectral index (BIS) on TTM-treated patients reported significantly higher BIS values in the good outcome group compared to the poor outcome group[151-156]. A BIS value of ≤6, corresponding to a suppressed or low-voltage EEG, at some point during TTM was strongly but not invariably associated with a poor outcome[151-153,156].

Three studies using suppression-ratio (degree of discontinuity) on TTM-treated patients reported significantly lower suppression-ratios in patients with good outcome compared to patients with poor outcome[142,155,156]. One of these studies reported a specificity of 100% to predict a poor outcome for suppression-ratio ≥22% at 48 hours after CA[142]. This latter study also reported significant differences in two kinds of entropy measurements comparing the two outcome groups[142].

Snap shots or trends?

cEEG monitoring generates vast amounts of EEG data and the specific data that is reported varies among studies. For instance, whether the best[85], worst[131] or dominating background patterns are reported during a certain time period varies, or the strategy for choosing is not reported. Also the duration of the evaluated time periods around each reported time point varies from a few minutes[144] to several hours[85]. Choosing the best background pattern over a longer period would probably be less affected by fluctuations in sedation, amount of artefacts, etc.

Summary (cEEG background predictors of poor outcome)

After rewarming and weaning of sedation corresponding to approximately 48 hours after CA, generalized suppression and burst-suppression are strongly associated with a poor outcome in studies using cEEG with or without TTM-treatment[131,134,137,143,148]. Residual sedation was affecting all false positives with burst-suppression in one study[150]. A liberally defined burst-suppression pattern or

even a suppressed background during ongoing TTM and sedation should not be considered a highly malignant sign. Further research is needed to investigate if "malignant burst-suppression patterns" could be strictly defined during ongoing TTM and sedation.

Malignant bursts

Several studies report that if certain malignant features accompany a burst-suppression pattern the reliability to predict a poor outcome increases and prognostication can possibly be performed even during ongoing TTM.

Identical bursts

A malignant feature that seems very promising is identical bursts, defined as identical shapes of the initial part (500ms) of subsequent burst in a burst-suppression pattern.

Several recent studies from two separate research groups explored the prognostic significance of a strictly defined burst-suppression with identical bursts and reported no false positives in two relatively large cohorts[134,144,157,158]. One of these studies also reported that half of their patients with burst-suppression with identical bursts also had myoclonus time-locked to the bursts[134].

Burst-suppression with identical bursts appeared at a median of 12 hours (range 3-23) after CA. It was always a transient pattern and evolved into less specific patterns at a median of 36 hours (range 15-53) after CA. Therefore, cEEG monitoring during the first two days after CA is the most reasonable method to detect the pattern. Interrater agreement for identifying identical bursts between two interpreters from the same group was substantial. Further, a quantitative measurement to assess the degree of burst shape similarity, with defined cut-off values, was developed to further enhance reliability[158].

When comparing burst-suppression with identical bursts after CA to burst-suppression without identical bursts, in EEGs deriving mainly from anesthetized patients, there were several differences. The identical bursts were more often synchronous (100% versus 64%), of higher maximum amplitudes (128 versus 25 μV), suppression periods were always totally suppressed and all transitions between bursts and suppression periods were abrupt[158]. Some of these latter characteristics, for instance high-voltage bursts, have been used in the definition of burst-suppression by other groups that reported a relatively high specificity to predict a poor outcome even during ongoing TTM[146,149,159], but the new concept of identical bursts seems to be a more reliable predictor.

Epileptiform bursts

A burst-suppression with generalized epileptiform activity has been proposed to be strongly associated with poor outcome in non-TTM-treated patients[53], but the phenomenon has often been evaluated as part of grading scales and not in isolation[118,122,123].

In burst-suppression induced by commonly used sedatives sharp components are often seen. When using anesthesia with gas (sevoflurane) even epileptiform activity has been described in healthy subjects[142]. Further, periodic epileptiform discharges have also been reported when lowering the body temperature just below the range commonly used in TTM[77]. These factors do not likely affect the prognostic significance of a burst-suppression with clear epileptiform activity after CA but this has to be explored further in TTM-treated patients.

Bursts time-locked to myoclonus

The clinical entity of myoclonus can appear together with various EEG patterns, but most often a burst-suppression pattern[119].

Burst-suppression with bursts appearing time-locked to clinical myoclonus, observed on video or by concomitant muscle artefacts, has been reported to be strongly associated with a poor outcome with no false positives reported[134,143,150,160]. If ongoing for >30 minutes some authors term this phenomenon myoclonic status epilepticus[150,160], even during burst-suppression when unequivocal electrographic seizure activity is lacking, and reported no false positives. Other groups avoid the term myoclonic status epilepticus[159].

Electrographic discharges

Electrographic discharges after CA, ranging from sporadic epileptiform discharges to unequivocal electrographic status epilepticus, have been explored in several studies, most of them used cEEG monitoring.

Lowering the body temperature during TTM has antiepileptic effects *per se*[161,162]. In addition, the sedation used during TTM also has clear antiepileptic effects. Still epileptiform discharges and even electrographic seizure activity may occur during TTM.

Clinical correlate

Clinical convulsions, regardless of EEG correlates, are found in approximately one third of post CA patients[35]. Nonconvulsive seizures occurred in 19% of patients in a large heterogeneous cohort of critically ill patients with different aetiologies[163].

This is in line with studies on TTM-treated CA patients monitored with cEEG that found nonconvulsive seizures in 9-30%[131,164,165]. These studies reported that most electrographic seizures were nonconvulsive whereas other studies reported the opposite[85,166]. Differences in electro-clinical correlates may partly be explained by differences in protocols regarding sedation and neuromuscular blockade.

Inconsistent definitions

The prognostic significance of epileptiform activity and electrographic seizure activity has been explored in several studies after CA. However, definitions were inconsistent among the studies. This is not surprising since there is no universally accepted electrographic definition of seizure activity. For research purposes ACNS proposed criteria for unequivocal seizure activity, but states that a pattern not fulfilling these strict criteria still may or may not represent seizure activity in a given patient[57].

Electrographic status epilepticus and periodic discharges

In TTM-treated and non-TTM-treated comatose post CA patients the presence of electrographic status epilepticus (ESE), regardless of using conservative ("prolonged unequivocal seizure activity") or liberal ("abundant repetitive epileptiform activity or periodic discharges") definitions is strongly but not invariably associated with poor outcome in both routine EEG studies[111,115,136,167-171] and cEEG studies[85,142,160,164,166,172,173].

Using multivariate analyses ESE has been proposed as an independent predictor of poor prognosis[167]. Periodic discharges have also been reported to be an independent predictor of poor prognosis in patients with diverse acute brain illnesses[174,175].

It is controversial whether periodic discharges in CA patients may represent ongoing seizure activity and the pattern does not fulfill unequivocal seizure criteria according to the ACNS terminology. Since these patterns can be ictal, postictal, interictal or simply a marker of severe encephalopathy and their exact significance is poorly understood the term ictal-interictal continuum has been used[176].

Using mathematical models it has been hypothesized that periodic discharges might be generated by selective vulnerability of inhibitory cortical interneurons to ischemic damage leading to disinhibition and pathological synchronization of cortical pyramidal neurons[177].

Treatment strategies for status epilepticus vary considerably between institutions and prognosis is dependent on the underlying etiology[178]. This is particularly true in the postanoxic situation where consensus on definitions and treatments for ESE are lacking and prognosis is dependent on the extent of brain injury.

Characteristics of surviving ESE patients

Several patients with ESE and eventual good outcome have been reported. These patients had ESE debuting after rewarming. During ongoing ESE other favourable signs in the EEG, clinical examination or in other prognostic tools were found. Examples of favourable signs in this context are preserved EEG reactivity to stimuli, preserved brain stem reflexes, low levels of biochemical markers of brain injury, i.e. neuron specific enolase, and preserved N20-potentials on median nerve SSEP[173,179,180]. Two studies reporting ESE in the absence of EEG reactivity to stimuli reported a poor outcome for all their patients[166,179]. In other words lack of ominous signs that indicate an extensive brain injury in the multimodal assessment may be the strategy to identify ESE patients with a chance of a good recovery[181].

Summary (electrographic discharges)

Further studies are needed to investigate epileptiform activity after CA according to the ACNS EEG terminology and its relation to clinical convulsion and prognosis and whether treatment is beneficial. It seems clear that electrographic seizures provides prognostic information but the most crucial questions are whether electrographic seizures are an epiphenomenon after CA or if they *per se* significantly contribute to impaired consciousness or brain injury and thereby worsening outcome?[163]. Using multimodality brain monitoring might answer these questions. A recent case report demonstrated dramatic reductions in brain tissue oxygen tension and increase in cerebral blood flow time-locked to postanoxic electrographic seizures[182]. Further studies using multimodality monitoring are needed as well as controlled randomized trials.

Aims of the thesis

This thesis is focused on the prognostic value of EEG in comatose patients resuscitated after cardiac arrest who received TTM. The specific aims are:

- To evaluate EEG patterns at different time points in relation to outcome using simplified cEEG monitoring (paper I).
- To plan and describe the study design for the evaluation of routine EEGs in the TTM trial (paper II).
- To investigate inter- and intrarater variability of routine EEG patterns (paper III).
- To evaluate if a highly malignant EEG (suppression without discharges, suppression with continuous periodic discharges or burst-suppression) after rewarming is always associated with a poor outcome (paper IV).
- To evaluate the prognostic value of a malignant EEG (abundant periodic discharges, abundant rhythmic discharges, unequivocal seizure, discontinuous background, low-voltage background, reversed anterior-posterior gradient or unreactive background) and a benign EEG (absence of all malignant features) after rewarming (paper IV).
- To describe if there are any significant differences in prognostic value of routine EEG patterns after rewarming comparing patients who received TTM at 33°C and 36°C (paper IV).
- To describe if there are any significant differences in prognostic value of routine EEG patterns after rewarming comparing patients with and without ongoing sedation during EEG recording (paper IV).

Methods

The studies of this thesis are based on two patient cohorts included during different time periods, the coma project 2004-2008 and the TTM trial 2010-2013.

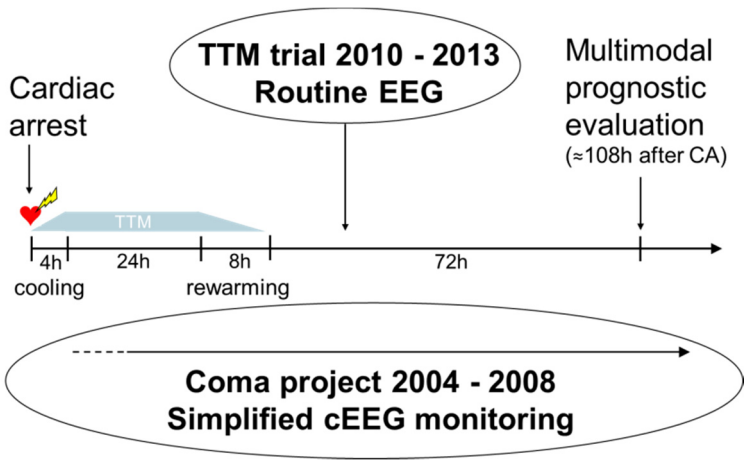

Figure 6. Study design
Simplified continuous EEG monitoring was performed in the coma project. A routine EEG was included in the protocol in the TTM trial.

Simplified cEEG study within the coma project (Paper I)

Background

TTM was introduced in southern Sweden 2002-2003 and all patients were prospectively evaluated in the multidisciplinary "coma project".

In 2004 simplified cEEG monitoring was introduced in the general ICU at Skane university hospital in Lund for TTM-treated patients. Consecutive patients from January 2004 until January 2008 were included in the simplified cEEG study (paper I).

Protocol

The study was approved by the ethics committee at Lund University.

After ROSC adult patients with sustained coma regardless of location and cause of CA or presenting rhythm were considered for TTM.

Eligible patients received cardiac angiography. In the ICU, the patients received mechanical ventilation, sedation (propofol or midazolam and fentanyl) and intermittent muscle relaxation.

TTM was induced with cold saline followed by use of an external or intravenous cooling system. Body temperature was maintained at 33°C for 24 hours followed by controlled rewarming over 8 hours. Sedation was reduced or stopped at the time point when normothermia was resumed. Treatment of clinically visible convulsions was recommended.

Active intensive care was continued at least until prognostication 72 hours after rewarming, which included neurological examination, median nerve SSEP and in selected cases brain MRI and routine EEG. WLST was allowed for GCS motor 1-2 or bilateral absence of N20 potentials. In patients not fulfilling these criteria intensive care was continued and WLST performed in the absence of improvements.

Patients were assessed using the CPC scale at discharge and at follow-up at six months. Primary outcome measures were return of consciousness during hospital stay and secondary measures were CPC grade at six months.

cEEG study design

On arrival to the ICU simplified cEEG monitoring was applied by the nursing staff using subcutaneous needle electrodes. Both the original EEG and the aEEG trends were displayed as two bipolar channels (C3-P3, C4-P4). The simplified montage is shown in figure 7. In the initial 34 patients (pilot study) the EEG data was blinded to the attending physician but thereafter an EEG specialist reported back once daily.

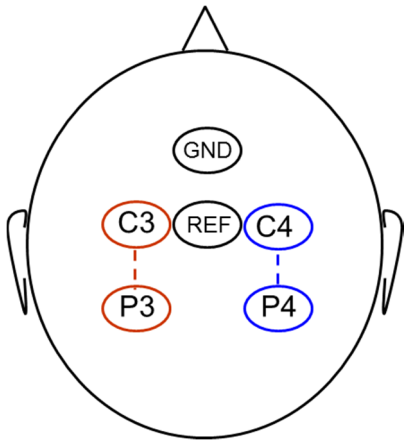

Figure 7. Simplified electrode montage used in paper I.

In the pilot study of 34 patients the aEEG levels were primarily used to define the patterns[85]. In the present study the original EEG traces was used to define the patterns and aEEG was only used to support interpretation over long periods and therefore the term simplified cEEG monitoring is used in this thesis.

The EEG patterns were defined from the original EEG and categorized into four patterns:

- Flat (extremely low-voltage background <10μV)
- Burst-suppression (high-voltage >50μV bursts of slow waves with sharp transients interrupted by suppression periods <10μV with duration >1sec)
- Continuous background
- Electrographic status epilepticus (repetitive epileptiform activity ≥1Hz recurrent or continuously for >30 minutes)

Whether ESE evolved from a continuous background or burst-suppression was determined (figure 8 and 9).

The cEEG data was retrieved to a database.

An EEG specialist blinded to clinical data evaluated the EEG patterns at the start of registration, at the time point of normothermia and 24 hours after normothermia. The whole monitoring period was screened for occurrence of ESE.

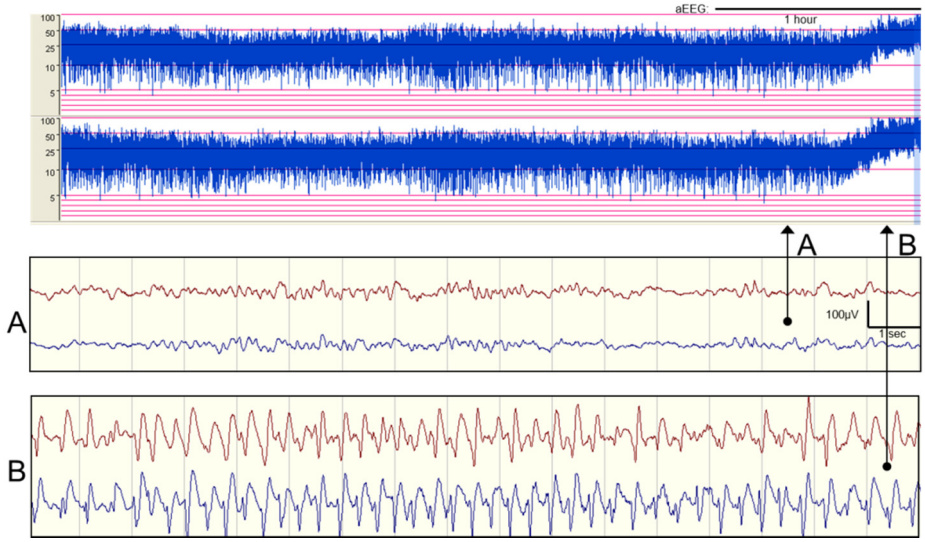

Figure 8. ESE from continuous background
Repetitive epileptiform discharges (≥1 Hz, >30 minutes) (time point B) consistent with electrographic status epilepticus (ESE) evolving from a continuous background (time point A). The original EEG traces are seen in the lower panels at a time scale of 1 second per division. The amplitude integrated EEG trend curves in the upper panels present an overview of 4 hours.

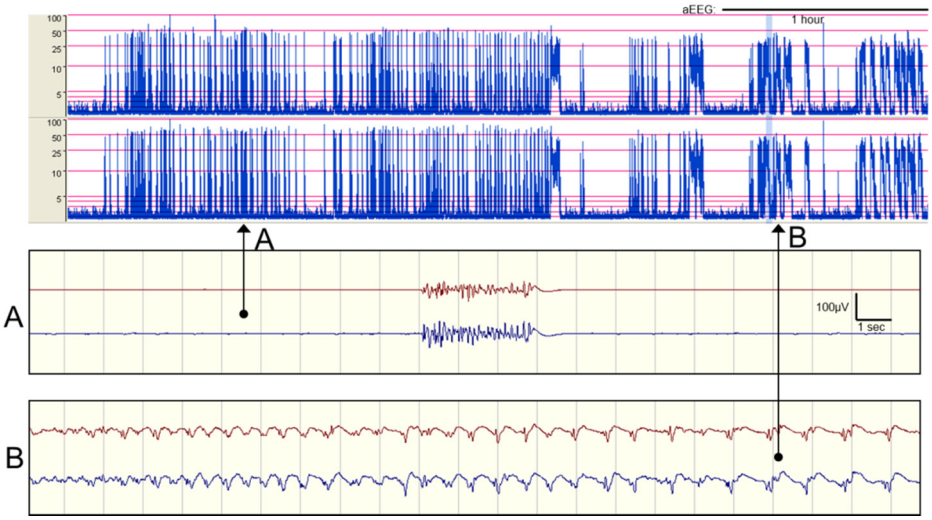

Figure 9. ESE from burst-suppression
Repeated unequivocal electrographic seizures >30 minutes (time point B) consistent with electrographic status epilepticus (ESE) evolving from a burst-suppression background (time point A).

Statistical methods

Fischer exact test was used to compare frequencies of categorical data. The Man-Whitney U test was used to test differences in start time (continuous data) of ESE between the two types of ESE. Predictive values were calculated for the EEG patterns at different time points.

Routine EEG study within the TTM trial (Paper II-IV)

Background

The Target Temperature Management trial (TTM trial) was an international clinical trial that randomized 950 comatose CA patients from November 2010 to January 2013 to a controlled temperature of 33°C or 36°C and found no significant differences in mortality or neurological outcome between the two groups[35].

Protocol

The TTM trial protocol[183] was approved by ethics committees in all participating institutions.

After ROSC adult patients with sustained coma after out-of-hospital CA of presumed cardiac cause regardless of presenting rhythm were randomized to target temperature 33°C or 36 C° for 24 hours followed by 8 hours of controlled rewarming to 37°C. Apart from level of controlled temperature the intensive care protocol was similar to that described above in the coma project.

Prognostication and WLST in the TTM trial were protocolized. At 72 hours after rewarming a physician blinded to the level of target temperature performed a neurological evaluation. Criteria that allowed WLST at this time point were persisting deep coma (GCS motor 1-2) combined with either bilateral absence of N20-potentials on median nerve SSEP or a treatment refractory status epilepticus. In addition, a clinical finding of status myoclonus during the first day in combination with bilateral absence of N20-potentials after rewarming allowed WLST. In patients not fulfilling these criteria intensive care was prolonged and patients were re-evaluated daily. The local EEG report was not blinded to the treating team. Survivors were assessed with the CPC scale during hospital stay, at discharge and at follow up at six months. In the EEG study a poor neurological outcome was defined as a best achieved CPC of 3-5.

Routine EEG study design

The rationale and study design of the evaluation of routine EEGs in the TTM trial is described in detail in paper II.

In the TTM trial a routine EEG was performed according to the protocol in patients who were still comatose 12-36 hours after rewarming, corresponding to approximately 48-72 hours after CA. All 36 TTM sites performed routine EEGs.

The EEGs were retrieved to a central database.

For paper III and IV all patients from eight selected TTM sites were included since these sites were able to export EEG data that allowed assessment of reactivity to external stimuli. Patients that died or awoke before the recommended time point of EEG were excluded. The routine EEGs were full-length (> 20 minutes) and at least 16 EEG channels were used.

Four EEG specialists from different European countries, blinded to clinical data, independently classified the EEGs according to the ACNS EEG terminology using an electronic case report form (eCRF).

The EEGs were classified into:

- Highly malignant EEG (figure 10)
    - Suppression without discharges
    - Suppression with continuous periodic discharges
    - Burst-suppression with or without discharges
- Malignant EEG
    - Abundant periodic discharges
    - Abundant rhythmic discharges
    - Unequivocal seizure
    - Discontinuous background
    - Low-voltage background
    - Reversed anterior-posterior gradient
    - Unreactive background
- Benign EEG (absence of all malignant features)

The same four EEG specialists interpreted 20 of the EEGs twice, six months apart, for the purpose of assessing intrarater variability.

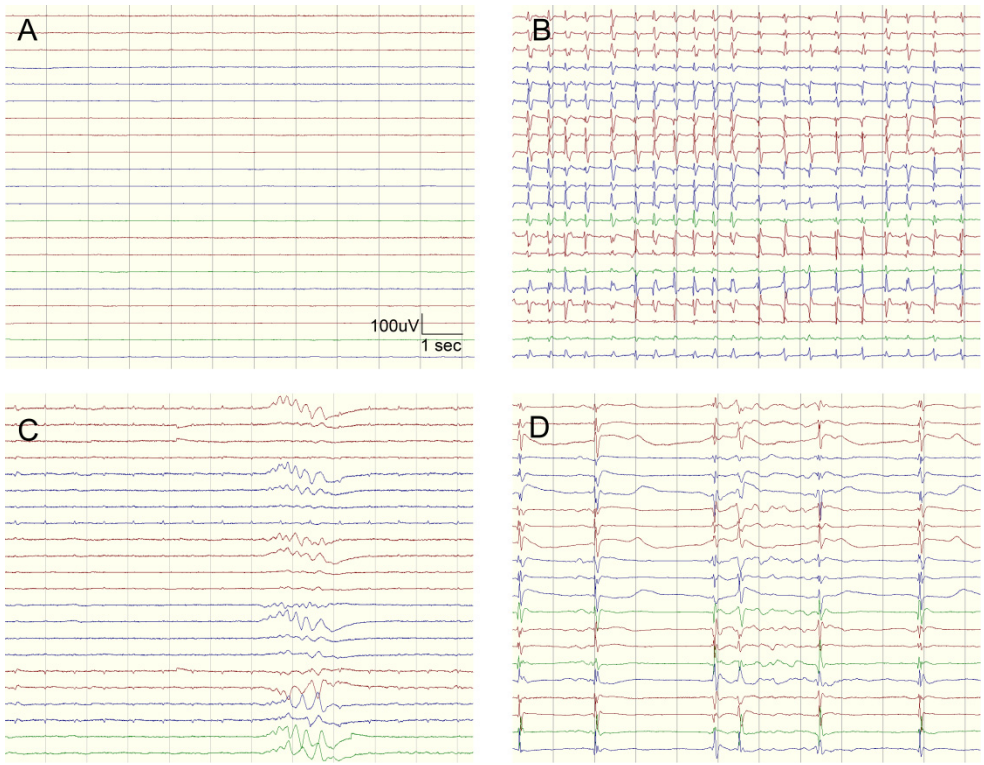

Figure 10. Highly malignant EEG patterns
(A) Suppressed background (amplitude <10μV, 100% of recording) without discharges. (B) Suppressed background with superimposed continuous periodic discharges. (C) Burst-suppression (periods of suppression with amplitudes <10μV constituting >50% of the recording) without discharges. (D) Burst-suppression with superimposed discharges.

Statistical methods

In paper III, interrater variability was evaluated using Cohen´s kappa and percent agreement. Percent agreement was defined as the proportion of the EEGs in which the interpreters reported identical findings, presented as agreement between all four interpreters and as the median of six pairs, formed by the four interpreters. Cohen´s kappa were calculated for the agreement within the six pairs and presented as median and range. Unweighted kappa was used for nominal (unordered categorical) variables and weighted kappa for ordinal (rank-ordered) variables. In paper IV, specificity and sensitivity of the patterns to predict a poor outcome were calculated and presented as the mode value for the four interpreters, i.e. the most common pattern reported. For comparisons between temperature groups, sedation and EEG patterns we applied generalized linear mixed models including interpretations from all four EEG specialists.

Results and discussion

Simplified cEEG study (Paper I)

Patient inclusion and characteristics

In total 111 patients received TTM. 16 patients were excluded because of aborted TTM, death before rewarming or no cEEG monitor available.

The remaining 95 patients were included in the EEG analysis. Of these patients 82 (86%) had out-of-hospital CA, 64 (67%) had a cardiac cause of arrest and 57 (60%) had initial shockable rhythm (VF or VT). The median time to ROSC was 20 minutes (IQR 14-30).

Thus, the cohort was heterogeneous regarding initial electrocardiogram rhythm, location and cause of arrest and included a high proportion of consecutive patients.

Outcome

Of the 95 patients 57 regained consciousness (best CPC 1-3) and the remaining 38 patients died without regaining consciousness (best CPC 4).

No patients were in a vegetative state after six months.

Best CPC and regaining of consciousness were reported according to guidelines[184].

Prognostication at start of cEEG

Simplified cEEG monitoring was started at a median of eight hours after CA (IQR 5-14) in the 95 patients.

Early continuous background

At start of monitoring 32 (34%) patients had a continuous background and 29 of these later woke up resulting in a predictive value for regaining consciousness of 91% (CI 75-98). Thus, an early debut of a continuous background during ongoing TTM was strongly associated with recovery of consciousness. This finding was subsequently supported by several other studies[131,134,137,143-146].

Early flat background

A flat pattern was seen in 47 (49%) patients and was not predictive of outcome since 26 (55%) of these patients regained consciousness. This observation that a large proportion of patients with a suppressed or low voltage background during the first 12 hours after ROSC had a good outcome is in line with the findings in the pilot study[85] and other studies using simplified[142,146] or multichannel EEG[73,134,143].

Early burst-suppression

An early burst-suppression pattern was seen in 14 (15%) of the patients and all died without regaining consciousness.

The definition of burst-suppression was relatively conservative demanding high-voltage bursts with sharp transients. The small sample size or the definition may explain the differences in outcome compared to other studies, which reported several survivors with good outcome among patients with an early and more liberally defined burst-suppression[137,142,143]. Other studies using the more conservative definition according to the ACNS EEG terminology also reported poor outcome for all their patients with burst-suppression, even during TTM[134,148].

Burst-suppression with identical bursts was recently proposed as a strong predictor of poor prognosis. Whether some of the patients with burst-suppression in the present study had identical bursts was not evaluated. The bursts in our study shared some common characteristics with identical bursts[158], for instance high-voltage and abrupt start from a flat background.

Prognostication at normothermia

Patients were rewarmed over eight hours and normothermia was resumed at a median of 36 hours after CA.

Recovery of a continuous background

After rewarming in total 62 patients had established a continuous background, of whom 54 regained consciousness and the other eight patients who remained unconscious either later developed ESE or had severe confounding factors. Thus debut of a continuous background at any time during TTM, without development of ESE, was still strongly associated with recovery of consciousness and had a predictive value for regaining consciousness of 87% (CI 76-94%).

Failure of electrographic recovery

The remaining 33 patients had flat, burst-suppression or ESE patterns and 30 of them had a poor outcome. Thus absence of a continuous pattern at normothermia was strongly associated with a poor prognosis and had a predictive value for poor outcome of 91% (CI 76-98). However, three patients with a flat pattern at normothermia restored a continuous background during the following day and regained consciousness. The reason for this unexpected finding is unclear. One factor could be residual or ongoing sedation still affecting the patients at normothermia, which can reduce amplitudes. Further, a flat pattern in a simplified montage is not equal to generalized suppression in a multichannel EEG, even if the amplitude thresholds are the same. In the good outcome patients the transition from a flat to a continuous pattern typically occurred over hours and during this transition period a low voltage discontinuous pattern was often seen. One hypothetical explanation for the discrepancy to other studies that reported suppression as a grossly abnormal sign already at 24 hours after CA[134,144] could be that the surviving patients in our study had a low voltage background, which was interpreted as a flat pattern in the simplified montage, especially if the signal-noise-ratio was not optimal.

Electrographic status epilepticus

The entire monitoring period was screened for ESE and 26 patients (27%) fulfilled the criteria for ESE at any time point. ESE had a predictive value for poor outcome of 92% (CI 75-99).

Two types of ESE

Two types of ESE were identified. One group of patients had ESE that developed from a burst-suppression pattern and all had a poor outcome. Another group of patients developed ESE from an already established continuous background and two of these patients survived with moderate and severe neurological disability at follow-up at six months.

ESE from burst-suppression started significantly earlier than ESE from continuous background ($p=0.01$) (figure 11). Typically, ESE from burst-suppression was more resistant to treatment and started during ongoing TTM whereas ESE from a continuous background started after rewarming. In both types of ESE there was an increased incidence of ESE around the time point of normothermia. Whether this could be explained by the concomitant withdrawal of sedation or TTM, which both have antiepileptic effect, is unknown.

Clinical convulsions

Clinical convulsions were seen in 25 of the 26 patients with ESE but varied in type, severity, and duration. The correlation in time to ESE was not systematically investigated, since all notations of convulsions were removed before interpretation to avoid bias. In addition to sedation, 22 patients received conventional antiepileptic drugs.

ESE definition

At the time of designing the present study, several criteria for seizure activity had been proposed and there was no consensus in the literature. During nonconvulsive status epilepticus the typical discharge frequency ranges from 1 to 3 Hz[185] and similar findings have been described during convulsive myoclonic status epilepticus[186]. Some of the proposed criteria for nonconvulsive electrographic seizures included repetitive epileptiform discharges along the ictal-interictal continuum if electrographic or clinical improvement was seen after treatment[187-189] or if the activity showed typical spatiotemporal evolution and reached 1 Hz[188,189]. In our pilot study, all patients with ESE also had clinical convulsions. If convulsions are time-locked to electrographic discharges most EEG specialists would regard the discharges as ictal[190].

For the definition of ESE using simplified cEEG in the present study we chose a conservative duration criteria (>30 minutes) but relatively liberal criteria regarding the rate of epileptiform discharges (≥1Hz). However, the number of patients with ESE in the present study was similar to other studies[164-166,179].

The definition of ESE in the present study included continuously appearing periodic discharges at a rate of 1Hz, which is controversial and is considered a pattern along the ictal-interictal continuum. However, in three recent studies of resuscitated patients frequency thresholds for defining periodic discharges as ESE spanned from 0.5 Hz[172] to 2.5 Hz[160] and 3 Hz[150].

The proportion of patients that fulfilled unequivocal seizure criteria according to the ACNS EEG terminology[57] was not assessed in the present study.

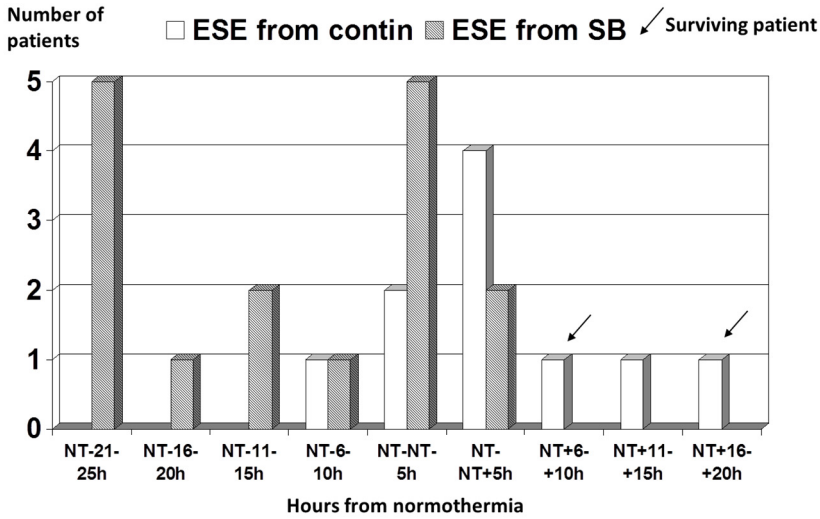

Figure 11. Time point of ESE debut.
Debut of electrographic status epilepticus (ESE) in relation to the time point of resumed normothermia at approximately 36 hours after the arrest. ESE that developed from a suppression-burst (SB) background started significantly earlier than ESE that developed from a continuous background. The arrows indicate two surviving patients with ESE.

Strengths and limitations

Strengths of the study are that nearly all consecutive patients were monitored early during TTM and the EEG analysis was performed blinded to outcome with pre-defined definitions relating to the original EEG traces and thereby increasing transferability of the results.

Limitations of this single center study are that blinding of the treating physician was not performed after the pilot study, video for correlation to convulsions was not available and a simplified montage was used making testing of reactivity impossible. We also acknowledge that some focal electrographic seizures may have been missed using the simplified montage. However, CA patients have a high proportion of periodic or rhythmic patterns with a generalized (86%) field (Paper III).

Simplified cEEG prognostication

In conclusion, simplified cEEG monitoring is easily applied bedside and provides early positive and negative prognostic information and can be used to screen for ESE, which have therapeutic implications.

The main findings were that an early continuous background predicts good outcome. An early ESE developing from burst-suppression predicts poor outcome whereas some patients with a late debut of ESE from a continuous background may survive (figure 12).

An early indication of prognosis is important for planning the patient care, for information to relatives and for deciding when other prognostic tools should be used. For instance an early positive prediction may lead to more aggressive treatment of cardiac or other organ failure. On the other hand an early negative prediction may lead to avoidance of futile invasive procedures and may be used to prepare relatives before the definitive prediction that is performed at least three days after CA, according to recent guidelines[36]. Our opinion is that simplified or multichannel cEEG is a valuable component in a multimodal strategy to continuously evaluate prognosis and cerebral function after CA[84,191].

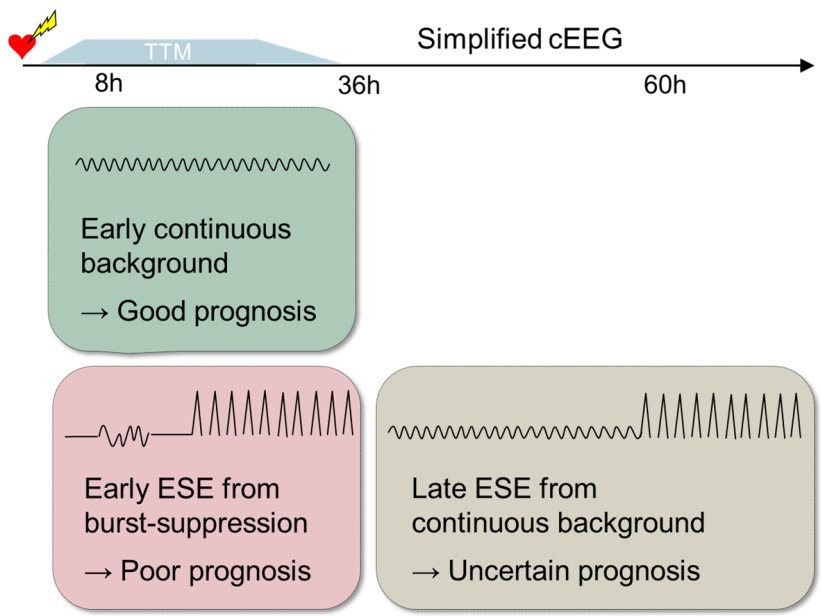

Figure 12. Simplified cEEG prognostication
An early continuous background predicts good outcome. An early electrographic status epilepticus (ESE) developing from burst-suppression predicts poor outcome whereas some patients with a late debut of ESE from a continuous background may survive.

Routine EEG study (Paper II-IV)

Patient inclusion and characteristics

In total 399 EEGs were performed at the 36 TTM sites. At the eight selected TTM sites 202 patients were randomized in the trial, of whom 22 died and 69 woke before prognostication and were excluded from the EEG study. In eight patients with prolonged coma an EEG was not performed, of whom one was brain dead, two had absent N20-potentials and in five the reason for missing EEG was unclear. The remaining 103 patients had a routine EEG at a median 77 hours (IQR 53-102) after CA and were included in the EEG analysis.

The selection of sites that were able to export EEG data on reactivity limits the power of the study but allows for homogenous high-quality data to test all our hypotheses.

Previous studies of TTM-treated patients have reported that approximately one third of patients are still comatose three days after rewarming corresponding to the time point of prognostication in the TTM trial[181]. Therefore the proportion of patients that had an EEG in the trial is close to the expected and likely compose a representative cohort of patients eligible to prognostication.

The recommended time point of a prognostic EEG recording was beyond 12 hours after rewarming during office hours. The reason for this choice was that we wanted to avoid recording during ongoing TTM and allow for weaning of sedation that was stopped after rewarming unless needed for intensive care reasons or treatment of ESE. However, we chose to include all EEGs that were performed after rewarming regardless of ongoing sedation in our main analysis and analyzed the effect of sedation on prognostic ability separately.

All of the 103 patients included in the EEG analysis had out-of-hospital CA of presumed cardiac cause and 74 (72%) had initial shockable rhythm (VF or VT). The median time to ROSC was 30 minutes (IQR 21-45). Thus, the cohort was more homogenous compared to the patients included in the previous coma project.

On the day of EEG recording the majority of patients were deeply comatose (median GCS motor 2). During ongoing EEG recording 16 patients (16%) had clinical convulsions, 37 (36%) were sedated and 36 (35%) had antiepileptic medication.

Outcome

Of the 103 patients 76 patients (74%) had a poor outcome (best CPC 3-4).

The exclusion of early awakening patients, with good prognosis[192], explains the high proportion of patients with poor outcome in the present EEG study compared to the main TTM trial[35].

Highly malignant EEG

A highly malignant EEG was reported by the majority of the four EEG specialists (mode value) in 38 patients (37%) and all had a poor outcome (table 1). The strength of agreement among the interpreters for identifying a highly malignant EEG was substantial (κ 0.71). Sensitivity varied slightly among the interpreters (mode value 50%, range 33-51) but importantly specificity to predict a poor outcome was 100% for all individual interpreters.

The highly malignant patterns used in this study adhere closely to previously described patterns strongly associated with a poor outcome[53].

Malignant EEG

Any malignant feature

A malignant EEG was reported in 89 patients (86%) and was defined as presence of at least one malignant feature and thus also included the highly malignant patterns (table 1). The strength of agreement between the interpreters for identifying a malignant EEG was only moderate (κ 0.42). This interrater variability may in part explain that sensitivity (mode value 99%, range 86-97) and specificity (mode value 48%, range 41-100) to predict poor outcome varied considerably among the EEG specialists.

These findings are important and discourage the use of an isolated malignant feature in prognostication and to support WLST.

Combinations of malignant features

If at least two malignant features from diverse subcategories (malignant periodic or rhythmic patterns; malignant background; unreactive EEG) were present in the same EEG, specificity increased significantly ($p<0.001$) to 96% (range 85-100), indicating that such combinations may have a prognostic value.

Low-voltage background

Considering the prognostic ability of different background voltage thresholds, the malignant pattern low-voltage background (<20μV) had several false positives (specificity 89%, range 70-100) whereas the highly malignant pattern suppressed background (<10μV) had no false positives for all four individual interpreters.

This finding is relevant since 20μV has been used as the threshold for predicting poor outcome in many studies[53-55,134,157].

Discontinuous background

Regarding the degree of continuity the malignant pattern discontinuous background had some false positives for two individual interpreters (specificity 100%, range 78-100) while the highly malignant burst-suppression had no false predictions.

Both assessment of voltage and continuity showed substantial interrater agreement among the four interpreters using the standardized definitions of ACNS (κ 0.65 and κ 0.76, respectively).

This is important since the most malignant grades used in classification systems after CA rely on assessment of these variables[118,133]. The diverse prognostic ability of burst-suppression and suppression reported in the literature[54,55] may in part be explained by diverse or undefined thresholds for voltage and continuity.

Unreactive background

There was only fair interrater agreement for identifying an unreactive EEG (κ 0.26), but the agreement varied considerably between pairs of EEG specialists (range κ 0.14-0.65).

This variation may reflect different traditions for evaluating reactivity in different centers. It is therefore not surprising that the specificity for an unreactive EEG to predict poor outcome varied considerably among the four interpreters (range 48-100%).

More strict definitions, video recordings, exact notations, neuromuscular blockade, automated assessment[139,140] or standardized stimuli[125] may possibly increase the reliability of reactivity assessment.

Rhythmic or periodic patterns or unequivocal seizure activity

Ongoing clinical convulsions during the EEG recording were present in 16 patients (16%), mostly myoclonus, and 37 patients (36%) had ongoing sedation.

A malignant periodic or rhythmic pattern was identified with substantial interrater agreement (κ 0.72) and was present in 33 patients (32%).

Five patients had unequivocal electrographic seizure activity and all had a poor outcome. Interrater agreement for identifying evolving patterns and plus modifiers, which renders the pattern more ictal-appearing[57], were only slight (κ 0.19 and 0.17, respectively) whereas the interrater agreement for the frequency of periodic or rhythmic patterns, that are included in most definitions of seizure activity, were substantial (κ 0.82).

Abundant periodic discharges were not inevitably associated with a poor outcome for the individual interpreter, but importantly all patients with periodic discharges superimposed on a suppressed background had a poor outcome.

Antiepileptic treatment was not protocolized and not included in the intervention of the trial.

The prognostic significance of occasional discharges was not assessed in the present study. A recent study included critically ill patients with diverse etiologies and used the ACNS terminology and found that prognosis was worse in patients with abundant or continuously appearing periodic discharges compared to a lower prevalence[175].

Benign EEG

A benign EEG, defined as absence of malignant features, was identified with moderate interrater agreement (κ 0.42) in 14 patients (14%). Of these, 13 (93%) had a good outcome. A benign EEG was found in only 1% of the 76 patients with a poor outcome.

This is an important finding since few predictors of a good outcome are available.

Table 1.
Prognostic ability to predict a poor outcome and interrater agreement of highly malignant and malignant patterns

EEG patterns:	**n=103** mode value (%)	**Sensitivity** mode value (95%CI)	**Specificity** mode value (95%CI)	**Specificity** range 4 raters	**Interrater agreement** kappa (κ)
≥1 highly malignant pattern[a]	38 (37%)	50 (39-61)	100 (88-100)	100-100	Substantial κ 0.71
Suppressed background without discharges	19 (18%)	25 (17-36)	100 (88-100)	100-100	-
Suppressed background with continuous periodic discharges	4 (4%)	5 (2-13)	100 (88-100)	100-100	-
Burst-Suppression (suppression >50%)	15 (15%)	20 (12-30)	100 (88-100)	100-100	-
≥1 malignant feature[b]	89 (86%)	99 (93-100)	48 (31-66)	41-100	Moderate κ 0.42
≥2 malignant features[c]	59 (57%)	76 (66-85)	96 (82-99)	85-100	-
Malignant periodic or rhythmic pattern	33 (32%)	43 (33-55)	100 (88-100)	96-100	Substantial κ 0.72
Abundant Periodic discharges	30 (29%)	40 (29-51)	100 (88-100)	96-100	-
Abundant Rhythmic spike-and-wave	4 (4%)	5 (2-13)	100 (88-100)	100-100	-
Unequivocal seizure	5 (5%)	7 (3-15)	100 (88-100)	100-100	-
Malignant background	69 (67%)	82 (71-89)	74 (55-87)	48-100	Moderate κ 0.44
Discontinuous (suppression >10%)	43 (42%)	57 (45-67)	100 (88-100)	78-100	-
Low-voltage	52 (50%)	65 (53-74)	89 (72-96)	70-100	-
Reversed anterior-posterior gradient	12 (12%)	13 (7-23)	93 (77-98)	78-100	-
Unreactive EEG[d]	65 (63%)	88 (78-94)	70 (48-86)	48-100	Fair κ 0.26

[a]Suppressed background without discharges; Suppressed background with continuous periodic discharges; Burst-suppression.

[b]Abundant periodic discharges; Abundant rhythmic spike-and-wave; Unequivocal seizure; Discontinuous background; Low-voltage background; Reversed anterior-posterior gradient; Unreactive EEG.

[c]From different malignant subcategories (Malignant periodic or rhythmic patterns; Malignant background; Unreactive EEG) present in the same EEG.

[d]Reactivity for both pain and sound stimuli was tested in 87 patients.

Level of target temperature

There were no significant differences between patients treated with 33°C compared to 36°C regarding prevalence or prognostic ability of highly malignant or malignant patterns. This is an important finding since questions have been raised whether the evidence from EEG studies before the introduction of TTM can be applied on TTM-treated patients even if the EEG recording was performed after rewarming.

Sedation

In 37 patients (36%) sedation was ongoing during the recording of EEG. The majority of these patients were sedated with propofol. Detailed data on the amount of sedation used was not available. There were no significant differences regarding the prognostic ability of highly malignant or malignant patterns to predict poor outcome comparing patients with ongoing sedation to those without ongoing sedation. The sample size is limited but nonetheless it is an important finding, since residual or ongoing sedation even in small doses often raises the question whether the prognostic information of EEG can be trusted at all.

Strengths and limitations

Strengths of the studies are that EEGs from a prospectively well-described cohort of consecutive patients from eight hospitals in four countries was studied blinded to outcome independently by four EEG specialists with different nationalities without prior collaboration. The rationale and study design were published before the EEG evaluation and a standardized EEG terminology was used. Before prognostic ability was analysed a study on inter- and intrarater variability was performed.

Limitations of the studies were that statistical power was limited by the exclusion of sites that could not export EEG data on reactivity and the exclusion of patients that died or woke up before the protocolized time point of EEG. Regarding prognostic ability, an important limitation was that the local EEG report was available to the treating team and although a treatment refractory status epilepticus was the only EEG criterion that allowed WLST if combined with deep coma the risk of a self-fulfilling prophecy cannot be excluded. On the other hand blinding of the EEGs would lead to a potential risk of missing subtle or nonconvulsive seizures. Regarding interrater variability, the study was not primarily designed and optimized to evaluate this question.

Routine EEG prognostication

In conclusion, routine EEG is generally available and the most common prognostic tool used to complement the clinical examination after CA.

All EEGs in the present study were performed after rewarming and the majority within two to four days after CA. Thus, our findings are representative for this time period only and it is well known that some of our malignant patterns can occur during the early phase of TTM among survivors with good outcome.

A highly malignant routine EEG after rewarming was identified with substantial interrater agreement and reliably predicted poor outcome in half of the patients without false positives for all four interpreters. Our strictly defined highly malignant patterns adhere closely to previously proposed negative predictors and are promising candidates to be incorporated in a multimodal prognostic algorithm.

An isolated finding of a single malignant feature was not a reliable predictor of poor outcome due to lack of specificity and interrater variability and should not be used in decisions on WLST. In this case prognostication primarily has to rely on other tools. However, combinations of at least two malignant features significantly increased specificity to 96% and if verified in another cohort it may be used to indicate a poor prognosis.

Neither the level of controlled temperature nor ongoing sedation in clinically used doses seems to significantly affect prognostic reliability.

If no malignant features were present, i.e. benign EEG, this was a strong predictor of a good outcome, which is an important finding since only few markers of a good prognosis are available.

The finding of a benign EEG can lead to cautiously optimistic information to relatives and be used to plan care and timing of other prognostic tools. For instance in the case of a benign and reactive EEG the patient may be given more time to wake up before additional prognostic procedures such as median nerve SSEP and MRI of the brain are considered, which can save resources in the case of later awakening. If other prognostic tools indicate a poor prognosis, a benign EEG may lead to prolonged observation.

Conclusions

In comatose patients resuscitated after cardiac arrest who received targeted temperature management (TTM):

- Using simplified cEEG – a continuous background early during TTM or at normothermia was highly predictive of recovery of consciousness.
- Using simplified cEEG – absence of a continuous background at normothermia was highly predictive of continued coma.
- All patients fulfilling our simplified cEEG criteria for electrographic status epilepticus (ESE) evolving from a burst-suppression background died without regaining consciousness, while two patients with ESE evolving from a continuous background regained consciousness.
- ESE evolving from a burst-suppression background started earlier (during hypothermia) than ESE evolving from a continuous background.
- Using standardized interpretation, a highly malignant routine EEG (suppression without discharges, suppression with continuous periodic discharges or burst-suppression) after rewarming was identified with substantial inter- and intrarater agreement and was a reliable predictor of poor outcome in this cohort.
- An isolated malignant routine EEG feature could not predict poor prognosis.
- A benign routine EEG after rewarming was highly predictive of good outcome.
- The prognostic ability of a routine EEG after rewarming was not significantly affected by the level of targeted temperature or ongoing sedation in clinically used doses.

Future directions

Future studies using simplified cEEG should adhere to the ACNS EEG terminology for interpretation of both background and rhythmic and periodic patterns. Standardized patterns at different time points should be correlated to outcome.

Sites performing multichannel cEEG after CA may down-sample the electrode montage to a simplified montage in patients having electrographic seizures to investigate sensitivity and specificity of seizure detection and reliability of prognostication.

The prognostic ability of a highly malignant routine EEG should be confirmed in another larger cohort. This can be done in the remaining patients in the TTM trial that were excluded from the present analysis.

The prognostic value of routine EEG should be compared with simplified cEEG and those two modalities should be compared with routine EEG and simplified cEEG in combination.

Further studies combining EEG with other prognostic tools are warranted.

Swedish summary / Populärvetenskaplig sammanfattning

Hjärt-kärlsjukdom är en av västvärldens stora folksjukdomar. I Sverige drabbas årligen cirka 10 000 personer av plötsligt hjärtstopp. Den vanligaste orsaken är att en akut hjärtinfarkt orsakar ett ”elektriskt kaos” i hjärtat. Vid ett hjärtstopp upphör blodförsörjningen till hjärnan, vilket leder till medvetslöshet inom några sekunder och inom några få minuter börjar hjärnan ta skada. Om man får igång hjärtat igen med hjälp av hjärtlungräddning och en hjärtstartare är personen oftast medvetslös. Den medvetslösa patienten förs till en intensivvårdsavdelning för andningsstöd med respirator och annan understödjande behandling. Ungefär hälften av dessa intensivvårdade patienter skrivs ut levande från sjukhuset och flertalet av dessa har inga eller lätta funktionsbortfall.

I syfte att minska hjärnskadan och förbättra överlevnaden sänks patientens kroppstemperatur på ett kontrollerat sätt i 24 timmar. Dock har det funnits en viss osäkerhet kring kylbehandlingens effekt och vilken temperatursänkning som är mest fördelaktig. Därför genomfördes 2010-2013 en ny stor internationell studie, *Target Temperature Management trial* (TTM-studien). Studien kunde inte finna någon skillnad i överlevnad eller neurologisk funktionsnivå mellan patienter som randomiserats till kontrollerad kroppstemperatur vid 33ºC jämfört med 36ºC.

I ett tidigt skede efter hjärtstoppet är det svårt att avgöra vilken grad av hjärnskada som den medvetslöse patienten har fått. Vissa patienter blir helt återställda medan andra vaknar med varierande grad av hjärnskada. En tredje grupp har en så allvarlig hjärnskada att de aldrig kommer att vakna oavsett behandlingsinsats.

För att tolerera kylbehandlingen behövs sederande läkemedel och ibland muskelavslappnade medel. Detta försvårar den kliniska prognosbedömningen de första dagarna och därför behövs ytterligare prognostiska verktyg.

Electroencefalografi (EEG) är viktig pusselbit i prognosbedömningen efter hjärtstopp och kan även upptäcka ”dolda” epileptiska anfall i hjärnan. EEG är en enkel och ofarlig metod för att mäta hjärnans elektriska aktivitet med hjälp av elektroder som fästs på huvudet. Vid ett hjärtstopp släcks hjärnans elektriska aktivitet ut helt inom några sekunder och patienten blir medvetslös. När sedan blodförsörjningen till hjärnan återställts kan man med EEG följa hur hjärnans elektriska aktivitet återkommer. Olika EEG mönster efter hjärtstopp har olika prognostisk betydelse. Dock har värdet av EEG som prognostiskt verktyg

begränsats av att flera olika klassifikationssystem använts och av bristande samstämmighet i tolkningen av mönstren mellan olika EEG specialister.

I samarbete mellan klinisk neurofysiologi (EEG-laboratoriet) och intensivvårds-avdelningarna i Skåne har rutiner utvecklats för att registrera förenklat EEG under en längre tid, så kallad kontinuerlig EEG övervakning.

En hjärnskada efter hjärtstopp ökar risken för epileptiska kramper, vilket drabbar cirka en tredjedel av patienterna. Dessa kramper döljs ofta av pågående medicinering och riskerar att förbli obehandlade. Kramperna beror på kaotisk elektrisk aktivitet i hjärnan som kan upptäckas med EEG och behandlas med krampförebyggande läkemedel.

Syftet med denna avhandling är att närmare undersöka det prognostiska värdet av EEG på kylbehandlade medvetslösa patienter efter hjärtstopp. Värdet av både kortvarig rutin EEG registrering samt förenklad kontinuerlig EEG övervakning som pågår i flera dygn har undersökts.

Mellan 2004 och 2008 undersökte vi 95 medvetslösa återupplivade hjärtstopps-patienter med förenklad EEG övervakning vid intensivvårdsavdelningen i Lund. Vi delade in patienterna i olika grupper beroende på hur deras elektriska hjärnaktivitet såg ut. Vi såg att förenklad EEG övervakning var ett kraftfullt verktyg för att tidigt bedöma prognos och för att upptäcka epileptiska kramper.

Som del i TTM-studien (2010-2013) utfördes rutin EEG registreringar på alla patienter som fortfarande var medvetslösa efter kylbehandlingen. Rutin EEG från 103 patienter granskades av fyra EEG specialister från olika Europeiska länder. Nyligen publicerades en standardiserad EEG terminologi av Amerikanska EEG specialister som vi bedömer kommer få stor spridning och acceptans internationellt. Denna terminologi, som inte tidigare använts på hjärtstopps-patienter, användes i vår studie för att klassificera EEG mönstren på ett fördefinierat sätt. Våra höggradigt elakartade EEG mönster identifierades med stor samstämmighet mellan våra fyra EEG tolkare. Mönstren var en stark markör för att förutspå gravt neurologiskt funktionsbortfall eller död. Däremot vaknade nästan alla de patienter som uppvisade ett godartat EEG mönster och de hade inga eller endast lätta funktionsbortfall vid uppföljningen ett halvår senare.

Sammanfattningsvis ger EEG tidig prognostisk information hos medvetslösa patienter efter hjärtstopp, som är viktigt för att kunna planera vården och ge anhöriga korrekt information. Hos alla hjärtstoppspatienter i Sverige övervakas hjärtats elektriska aktivitet med EKG. För oss är det lika självklart att man ska övervaka hjärnans elektriska aktivitet med EEG för att förbättra vården av dessa svårt sjuka patienter.

Acknowledgements

I would like to express my gratitude to the all the people around me who in different ways made this dissertation project possible!

First of all to Tobias Cronberg, my tutor, always supporting me and bringing me new challenges! With enthusiasm and encouragement you have taught me that in science no mountains are too high and no valleys are too deep to be crossed, even if the road is slippery, the rain is pouring down and nightfall is closing in. Thank you for all the lunches together with discussions on science and life! I look forward to a sailing trip in Öresund this summer to celebrate that you have put PhD hats on Gisela, Irina and me!

To Ingmar Rosén, my tutor in clinical neurophysiology and in particular simplified cEEG! Your guidance and expertise have been invaluable to the project! Thank you for supporting me a lot in the beginning of the project ten years ago and for letting me try my own wings gradually during this journey! Thank you for all the interesting scientific discussions on the mystery of EEG! Whenever there is a journal club or discussion going on at our department Ingmar comes around to share his wide experience, if he is not sailing in the archipelago in Blekinge.

To Hans Friberg, my co-tutor and guide in intensive care! Thank you for bringing me the perspective of the bedside intensive care physician! Usually I only encounter the ICU environment when reviewing video-EEGs. You have taught me to simplify the message, which is hard for a clinical neurophysiologist. I have become a better scientific writer thanks to your valuable support with the manuscripts. Thank you for all the parties with hats! You, Tobias and Niklas have developed our research group into something really great! Hop on Niklas racing sail boat and join the celebration this summer!

To Eskil Elmér, my tutor during the first year who saved the PhD project and gave me positive energy when my knowledge in InDesign was failing me.

To co-authors and friends in our research group; Malin Rundgren for helping me around in my first scientific project and for the impressive work of recording all the simplified cEEGs; Niklas Nielsen for steering the massive TTM ship and recruiting me as a seaman; Sofia Backman, Irina Dragancea and Gisela Lilja who I have worked closely together with in the "neuro-PhD-team of Tobias" and we have supported each other; And all others in the research group for interesting and enjoyable meetings!

A special thanks to all my colleagues and friends at the department of clinical neurophysiology in Lund/Malmö (see supplement “RS-ID anställda Klinisk neurofysiologi”!!!), for making every day at work a true pleasure and for supporting me in my journey towards my PhD!!!

To Andrea Rossetti, Troels Wesenberg Kjaer and Anne-Fleur van Rootselaar for interpreting all the routine EEGs and for sharing your expertise in the project.

To the co-authors in the TTM steering group and the EEG group of the TTM trial for letting me coordinate the EEG evaluations and for all your help with improving the manuscripts.

To all the TTM sites and EEG laboratories for making this EEG project possible and a special thanks to Copenhagen (Christian Hassager, John-Bro Jeppesen, Jesper Kjaergaard), Amsterdam (Janneke Horn), Linköping (Hans Lindehammar), Lund, Malmö and Helsingborg for including patients in the EEG substudy that will be the next project after my PhD (cliffhanger!).

To Susann Ullén for helping me with the statistics. To Bodil Persson, Ola Åkesson and Anne Adolfsson for helping me prepare the EEGs for analysis. To Gunnar Gunnarson, Lars-Johan Ahnlide, Björn Wallström and Baha Jabbar for technical support. To Bo Jönsson for generously letting me use his nice illustrations.

AND…..

To my beloved wife Johanna for all your love and support!!! Without you this journey would have been impossible! I really look forward to spending the rest of my life with you! This is a special year indeed, ten years ago we drove the Excalibur to the church in Döderhult and got married, ten years ago I started this science project and fourty years ago I was born! I really look forward to celebrating this with you on a paradise island in Thailand!!! I love you!!!

To my wonderful children Jakob and Elias for bringing happiness to my life every day! Sorry for borrowing your iPad to read articles all the time and I look forward to playing a lot more with you when this book is finished!

To my parents Sylvia and Sven for loving me and believing in me! You convinced me to apply for medical school in Lund – “Erik, you will enjoy taking a stroll through the park on the way to the lecture”. Thanks for all the short phone calls during the recent months just to check that I was alright!

To my dear parents-in-law Lisbeth and Jan-Åke and my sister-in-law Rebecka and David for love and support! I look forward to the baptism of Bianca this weekend!

To all my friends and relatives in Skåne and north of Hallandsåsen who will join the party tonight!

Financial support

This dissertation project has been made possible by generous grants from:

The European Union Interreg IV A programme, the Swedish Heart and Lung Association, the Skåne University Hospital Foundations, the Gyllenstierna-Krapperup's Foundation, Academy of Caring Sciences at Skåne University Hospital, the Swedish National Health System (ALF), the County Council of Skåne, the Swedish Society of Medicine, the Koch Foundation, the Swedish Heart-Lung Foundation, AFA Insurance Foundation, the Hans-Gabriel and Alice Trolle-Wachtmeister Foundation for medical research, the Segerfalk Foundation, AnnaLisa and S.E. Lundgrens Foundation, Laerdal Foundation and the Tryg Foundation.

We thank the publishers for permitting reprints in this dissertation; Wolter Kluwer Health, Lippincott Williams & Wilkins; Elsevier Ireland Ltd; Springer.

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Print and layout by Media-Tryck 2016
MILJÖMÄRKT Trycksak 341 903

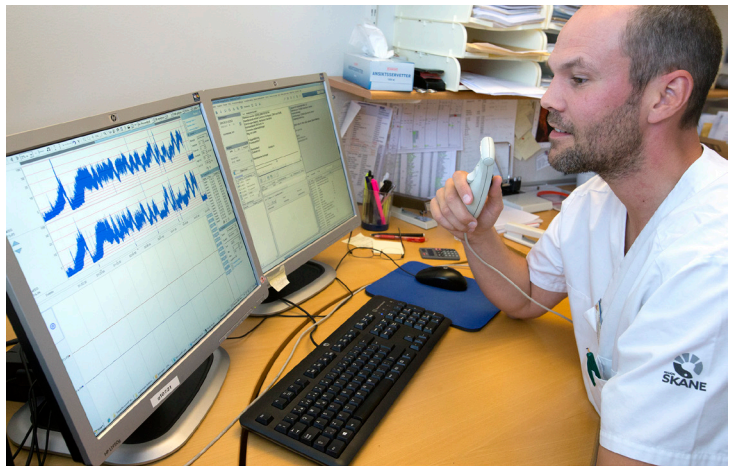

Photo by Roger Lundholm

Erik Westhall is a clinical neurophysiologist at Skane University Hospital, Sweden. This thesis is focusing on electroencephalography (EEG) in comatose patients resuscitated after cardiac arrest. In the picture he is interpreting an EEG and when he is not doing that he lives with his family in Lund and enjoys playing with his two children, floorball in the weekends and boatlife in the summer!

LUND UNIVERSITY
Faculty of Medicine

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2016:29
ISBN 978-91-7619-255-9
ISSN 1652-8220