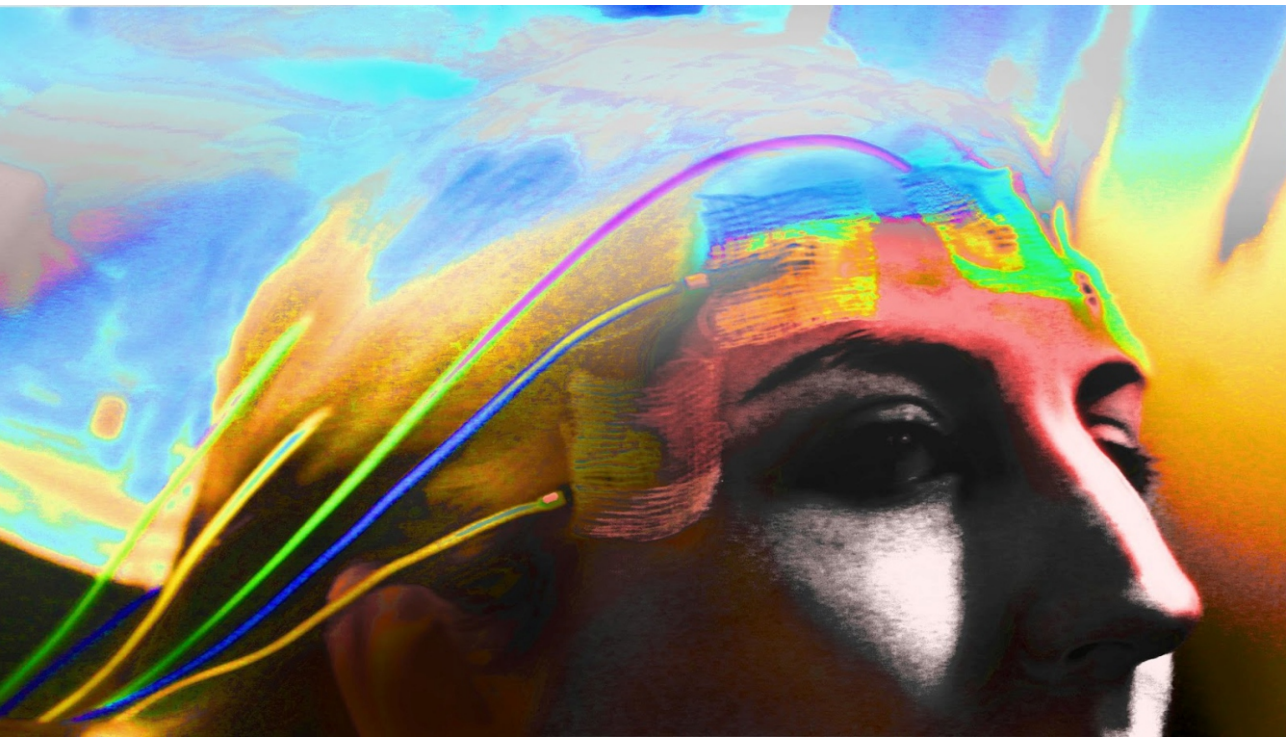
EEG monitoring
in postanoxic coma



Marleen Tjepkema-Cloostermans

EEG MONITORING IN POSTANOXIC COMA

EEG monitoring in postanoxisch coma

M.C. Tjepkema-Cloostermans

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The research presented in this thesis was done in the group Clinical Neurophysiology from the University of Twente, Enschede, and the departments of Clinical Neurophysiology, Neurology and Intensive Care from the Medisch Spectrum Twente hospital, Enschede, in collaboration with the Rijnstate hospital, Arnhem.

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EEG MONITORING IN POSTANOXIC COMA

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Chapter 1

General Introduction

Among all organs, the brain is the most dependent on continuous oxygen and glucose supply. At rest, the brain uses around 20% of the total energy consumption[1,2], while there are almost no energy reserves. Cerebral function fails within a few seconds after cessation of cerebral blood flow, and within 3 to 5 minutes cortical damage becomes irreversible[1]. Neurological injury caused by global ischemia is known as postanoxic encephalopathy. The severity of the postanoxic encephalopathy is mainly determined by the duration and depth of the decrease in cerebral blood flow. Therefore, in patients with cardiac arrest, the time from cardiac arrest to return of spontaneous circulation is very important for the neurological outcome[3]. Patients with postanoxic encephalopathy who do not immediately regain consciousness after restoration of blood flow are admitted to the intensive care unit (ICU) for further treatment. Despite intensive treatment, in 50–60% of these patients consciousness will never return due to severe ischemic brain injury[3,4].

Early pathophysiological processes during ischemia include functional neuronal impairment, which is followed by structural failure in a later stage. The first functional process to fail is synaptic transmission[2], which requires about 44% of the brain's energy consumption[5]. In mild ischemia, failure of synaptic transmission might be the only effect[2]. The changes of synaptic function are assumed to be reversible if blood flow is restored in time, however prolonged ischemia can lead to persistent synaptic failure[2,6,7]. When the other energy dependent processes fail as well, cell swelling will occur, which eventually will lead to cell death.

The only treatment of proven benefit to improve outcome in patients with postanoxic encephalopathy is mild therapeutic hypothermia[8–10]. During mild therapeutic hypothermia the body temperature is actively lowered to 33°C for

a period of 24 hours. Treatment with hypothermia protects the brain against secondary ischemic injury by affecting various steps of the ischemic cascade. Hypothermia affects several metabolic pathways, inflammatory reactions and apoptosis processes, and it promotes neuronal integrity[10].

During hypothermia and passive rewarming till normal body temperature afterwards, patients are sedated. Once a patient is at normothermia, sedation is stopped. If the patient does not awake after rewarming, the clinicians are confronted with the question whether the remaining neurological injury is still reversible. At some point, the treating clinician has to make the difficult decision whether continuation of medical treatment is still worthwhile. Early and reliable prediction of the neurological outcome is therefore highly relevant and can prevent unjustified discontinuation of medical treatment as well as continuation of futile medical treatment. Thereby, it decreases unnecessary ICU stay and medical costs, and shortens the time of uncertainty for the patient's family.

In patients treated with hypothermia neurological evaluation is limited. Several studies showed that the use of clinical parameters, such as the motor score, have become unreliable as prognostic parameters since the introduction of therapeutic hypothermia[11–14]. Also the use of biochemical parameters (with the current cut-off values) has become less reliable since the introduction of hypothermia[13,15,16]. A possible explanation for the lower reliability of these clinical and biochemical markers might be the long time that is needed before the sedatives are completely worn off in these patients. The use of imaging methods is not without risk in ICU patients, because the patients have to be transported from the ICU to the scanner. Furthermore, imaging methods give only a snapshot of the dynamic ischemic process. Even more important, with imaging methods only structural failure can be observed, while functional failure is not assessed. Clinical neurophysiology has provided two techniques, which do allow evaluation of the functioning of the nervous system in these patients: the somatosensory evoked potential (SSEP) and the electroencephalogram (EEG).

Somatosensory evoked potential

The somatosensory evoked potential (SSEP) is a small electrical signal (<10–50 μV) that can be recorded non-invasively from the skull, after giving a set of electrical stimuli to one of the peripheral nerves. Measurement of the SSEP evaluates the complete pathway from the peripheral sensory nervous system

to the sensory cortex that runs via the dorsal column lemniscal pathway via the spinal cord, brainstem and thalamus[17,18]. The earliest cortical potential is the N20, which is generated in the primary somatosensory cortex, where thalamocortical cells make synaptic connections with the superficial and deep pyramidal cell layers[19,20]. In comparison to the later cortical responses, the N20 is the most robust and is the latest waveform to disappear during increasing levels of encephalopathy. Furthermore, the N20 is relatively independent on the level of sedation[17].

Bilateral absence of the N20 has been identified as the most powerful predictor of poor outcome in patients who are unconscious after circulatory arrest not being treated with hypothermia, with a false positive rate of 0.7%[21,22]. In patients treated with therapeutic hypothermia, absence of the N20 at 72 hours after cardiac arrest also indicates a poor prognosis. In two large prospective studies, including 228 patients, the median nerve SSEP at normothermia was found to be a reliable tool to predict poor neurological outcome, with a false positive rate of 0%[12,23]. However, a retrospective study of Leithner in 122 available SSEPs revealed one patient treated with therapeutic hypothermia after cardiac arrest with bilateral absent N20 responses at day 3 with good neurological outcome[24]. Despite this single case, pooled analysis of these three recent studies[12,23,24] on cardiac arrest patients after hypothermia still gives a very low false positive rate of 0.9%, indicating that bilateral absence of the N20 should be viewed as a reliable predictor for poor outcome in patients treated with hypothermia.

Unfortunately, preservation of the N20 does not imply a favourable outcome in patients after cardiac arrest. In fact, only a small proportion of patients with a poor outcome after resuscitation has negative SSEP responses resulting in a low sensitivity of this parameter for the prediction of poor outcome. This low sensitivity might be explained by selective vulnerability of synapses. The N20 response is dependent on the thalamocortical synapses in the primary sensory cortex. Therefore, the SSEP does not give information on the functioning of the intra-cortical synapses, which are more vulnerable to ischemia[20].

Electroencephalography

The electroencephalogram (EEG) measures the spontaneous electrical activity of the brain through the skull. In general, the EEG measures potential differences originating from synaptic activity of the pyramidal cells of the cor-

tex[1]. Thereby the EEG directly reflects the functioning of cortical synapses, which is the process that is the most sensitive for ischemia. The dendrites of the pyramidal cells almost permanently receive synaptic input. This input induces excitatory or inhibitory postsynaptic potentials. Currents derived from synapses move through the dendrites and cell body to the axon and pass through the membrane to the extracellular space along the way, resulting in a current dipole. The electric activity generated by a single neuron is too small to be picked up by EEG. However, pyramidal cells synchronize their activity and the neurons in the cortex are uniformly oriented, perpendicular to the cortex, resulting in sufficiently large extracellular currents to allow recording of scalp potentials.

Since the EEG measures spontaneous brain activity, the EEG can be used at the bedside of the patient for continuous monitoring of the brain. In addition, the EEG has a high time-resolution. Evolution of EEG patterns, starting with the period during hypothermia, might therefore provide clinically relevant information regarding recovery from postanoxic coma.

Several studies indicated that EEG monitoring might have a role in the prognosis of neurological outcome. However, previously studied EEG characteristics varied widely and in most studies it is unclear at which time after cardiac arrest these were measured, which makes it difficult to convert these results into clinical guidelines. In general, continuous patterns are associated with good neurological outcome, both during hypothermia and at normothermia[12,25–28]. In contrast, flat EEGs, burst suppression EEGs and status epilepticus at normothermia are associated with poor neurological outcome[12,25–28].

One of the disadvantages of the EEG is the complexity of the signal. The EEG signals can only be reliably interpreted by an experienced electroencephalgrapher[29,30]. In a standard EEG, 19 channels of EEG registrations are displayed in pages of 10 seconds. Therefore, the interpretation of continuous EEG registrations of at least 24 hours is time-consuming[30–32]. To reduce the time needed for EEG interpretation, the addition of quantitative EEG analysis to the standard visual analysis of the EEG might play an important role[29–32]. Another advantage of quantitative EEG analysis is that it makes the analysis more objective[29,30].

Goals

This thesis is subdivided into three parts, each with its own corresponding goal. The first goal is to evaluate whether the EEG can improve the prediction of neurological outcome in patients after cardiac arrest. To be useful in clinical practice, the false positive rate of the EEG for predicting poor outcome should be 0% (or lower than 0.9% comparable to the false positive rate of the SSEP), while the sensitivity should be high. To have added value to the SSEP measurement, the EEG should at least correctly predict poor neurological outcome in some of the patients with present SSEP responses. In addition, we evaluate whether the EEG can be used for the prediction of good neurological outcome.

The second goal of this thesis is to evaluate whether quantitative EEG analysis can assist in the classification of EEG patterns and prediction of the neurological outcome in patients after cardiac arrest.

Describing and scoring the EEG for prognostic purposes can be very useful and gives us information on the severity of the ischemia. However, it is still a general and descriptive assessment of EEG patterns resulting from ischemia. Understanding the generation of specific EEG patterns increases the insight in the pathophysiological processes resulting from ischemia. The third goal of this thesis is to explore if computational modelling can help us to discover what type of brain injury is reflected by a specific EEG pattern.

Outline of thesis

Part I: Clinical Studies

In this part we describe our clinical studies in which we evaluated the prognostic value of continuous EEG registrations in patients with postanoxic coma after cardiac arrest. Chapter 2 describes a cohort of 60 patients in which we evaluated the prognostic value of continuous EEG registrations and SSEP measurements. Chapter 3 describes our analysis of a distinct EEG pattern, “burst-suppression with identical bursts”, and its potential prognostic role in these patients. Chapter 4 gives the results of a large cohort study to the prognostic value of EEG performed in two hospitals (Medisch Spectrum Twente, Enschede, and Rijnstate Hospital, Arnhem). In this study, in which we included 148 patients, we wished to confirm our earlier findings of Chapter 2, combined with the new criteria given in Chapter 3.

Increased use of EEG monitoring for prognostic purposes also leads to increased detection of electroencephalographic seizure patterns. However, it is unclear whether treatment of electroencephalographic seizure patterns with anti-epileptic drugs improves outcome in these patients[32–35]. Chapter 5 describes a retrospective study to the effect of treatment with anti-epileptic drugs in comatose patients after cardiac arrest with electroencephalographic seizures and status epilepticus.

Part II: Signal Analysis

Part II of the thesis describes the development and implementation of two automated systems for EEG analysis in the ICU. The first one, described in Chapter 6, is developed for ICU patients in general. With this method, a first classification of the raw EEG is made. The second one, described in Chapter 7, is made with the specific purpose of rating the EEG of comatose postanoxic patients for prognostic purposes.

Part III: Computational Modelling

Chapter 8 describes our study with a computational meanfield model to simulate generalized periodic discharges, which is a specific EEG pattern that is often observed in patients after acute global ischemia.

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Part I

Clinical Studies

Chapter 2

Continuous EEG monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: A prospective cohort study

M.C. Cloostermans, F.B. van Meulen, C.J. Eertman, H.W. Hom, M.J.A.M. van Putten

Crit Care Med, 2012; 40:2867–2875

Abstract

Objective: To evaluate the value of continuous electroencephalography (EEG) in early prognostication in patients treated with hypothermia after cardiac arrest.

Design: Prospective cohort study.

Setting: Medical Intensive Care Unit (ICU).

Patients: Sixty patients admitted to the ICU for therapeutic hypothermia after cardiac arrest.

Intervention: None.

Measurements and Main Results: In all patients continuous EEG and daily somatosensory evoked potentials (SSEP) were recorded during the first 5 days of admission or until ICU discharge. Neurological outcomes were based on each patient's best achieved Cerebral Performance Category (CPC) score within 6 months. Twenty-seven out of 56 patients (48%) achieved good neurological outcome (CPC 1–2). At 12 hrs after resuscitation, 43% of the patients with good neurological outcome showed continuous, diffuse slowed EEG rhythms, while this was never observed in patients with poor outcome. The sensitivity for predicting poor neurological outcome of low voltage and iso-electric EEG patterns 24 hrs after resuscitation was 40% (95% confidence interval (CI): 19%–64%) with a 100% specificity (CI: 86%–100%), while sensitivity and specificity of absent SSEP responses during the first 24 hrs were 24% (CI: 10%–44%), and 100% (CI: 87%–100%), respectively. The negative predictive value for poor outcome of low voltage and iso-electric EEG patterns was 68% (CI: 50%–81%), compared to 55% (CI: 40%–60%) for bilateral SSEP absence, both with a positive predictive value of 100% (CI 63%–100% and 59%–100% respectively). Burst suppression patterns after 24 hrs were also associated with poor neurological outcome, but not inevitably so.

Conclusions: In patients treated with hypothermia, EEG monitoring during the first 24 hrs after resuscitation can contribute to the prediction of both good and poor neurological outcome. Continuous patterns within 12 hrs predicted good outcome. Iso-electric or low voltage EEGs after 24 hrs predicted poor outcome with a sensitivity almost two times larger than bilateral absent SSEP responses.

Introduction

Mild therapeutic hypothermia (TH) improves the neurological outcome in comatose patients after cardiac arrest[1,2], nevertheless survival rates remain poor. In 40%–66% of patients treated with TH after cardiac arrest, consciousness never returns despite treatment[1–5]. Early identification of patients with poor neurological outcome can prevent continuation of futile medical treatment, decrease Intensive Care Unit (ICU) stay and medical costs, and shorten the time of uncertainty for the patient's family. Early and reliable prognostication is therefore highly relevant, and treating physicians are indeed often confronted with the question whether continuation of treatment is worthwhile[6,7].

However, early prognostication remains challenging, especially since the predictive values of clinical, biochemical, and electrophysiological parameters of poor outcome have become uncertain since the introduction of TH[8–12]. At present, only a bilateral absent short latency somatosensory evoked potential (SSEP) response is highly predictive[13–15], probably even at 24 hrs after resuscitation in patients treated with TH[3,16]. Unfortunately, only a small proportion of patients with a poor outcome after resuscitation have negative SSEP responses as the sensitivity is approximately 20%–25%. This results in continuation of treatment in a significant fraction of patients with eventually unfavorable recovery, motivating the need for more sensitive predictors. Clearly these predictors need to have a specificity of 100%, similar to bilateral absence of the SSEP.

The electroencephalogram (EEG) reflects part of the function of cortical neurons[17], which are the most sensitive for ischemia. It was recently found that absent EEG background reactivity to painful stimulation, was associated with poor outcome after cardiac arrest, predicting poor outcome with a sensitivity of 75% and a specificity of 100%[10]. Following transient cerebral ischemia a complex series of pathophysiological events occurs, that evolve in time[18,19]. Part of these changes and neuronal recovery can be observed with continuous EEG monitoring. Evolution of EEG patterns, starting with the period during therapeutic hypothermia, may therefore provide clinically relevant information regarding recovery from postanoxic coma.

We performed a prospective cohort study to explore if continuous EEG monitoring and the changes in the EEG dynamics may serve as improved predictors for neurological outcome in patients treated with TH after cardiac arrest.

Materials and Methods

Design

From June 2010 to July 2011 we conducted a single center, prospective cohort study in patients who were treated with TH after cardiopulmonary resuscitation. The study setting was the 18 bed general and 10 bed thorax intensive care unit (ICU) of the Medisch Spectrum Twente, Enschede, the Netherlands. The Institutional Review Board waived the need for informed consent for EEG monitoring during ICU stay. However, for additional electrophysiological and clinical evaluation after discharge from the ICU, local institutional review board approval and written informed consents were obtained.

Patients

Consecutive adult patients (age>18 yrs), who were resuscitated after a cardiac arrest, remained comatose, were admitted to the ICU, and received TH were included. Exclusion criteria were other neurological injuries such as brain hemorrhages or traumatic head injury, or any known history of severe neurological disorders, brain surgery or brain trauma.

Treatment

Patients were first evaluated by a cardiologist in the emergency department and treated according to current standard therapy. Patients were then transferred to the ICU for TH. According to our protocol, comatose survivors are treated with TH regardless of the initial cardiac rhythm or the location of arrest (in-hospital or out-of-hospital). Hypothermia of 33°C was induced and maintained for 24 hrs by intravenously administering 2 liters of cold saline and by using cooling pads. Thereafter, patients were passively rewarmed at a maximum of 0.5°C/hr to normothermia. According to local protocols, propofol and fentanyl or remifentanil were used for sedation and against shivering, until the body temperature had reached 36.5°C. Sedation was aimed at a level equivalent to a score of −4 (deep sedation) or −5 (unarousable) at the Richmond Agitation Sedation Scale (RASS)[20,21]. On indication, a nondepolarising muscle relaxant (rocuronium) was used intermittently to avoid compensatory shivering. The decision to give a muscle relaxant was made by the treating physician, and not based on the EEG. Stable patients who regained consciousness were extubated when they were able to protect their airway and the airway was patent.

EEG

EEG recordings were started as soon as possible after the patients' arrival on the ICU and continued up to 5 days or until discharge from the ICU. Twenty-one silver-silverchloride cup electrodes were placed on the scalp according to the international 10–20 system. Recordings were made using a Neurocenter EEG recording system (Clinical Science Systems, Voorschoten, the Netherlands). For practical reasons, EEG recordings were not started late at night. Instead, for patients admitted to the ICU after 11 p.m., the recordings were started the next morning at 7 a.m.

All EEG analyses were performed after the registrations. EEG data played no role in actual prognostication of outcome or treatment decisions. However, the treating physicians were not completely blinded to the EEG to allow treatment of epileptiform discharges. Treatment of epileptiform discharges was left at the discretion of the treating physician. Afterwards, 5 min EEG epochs were automatically selected every hour during the first 48 hrs after resuscitation and every 2 hrs during the remainder of the registration. All epochs were visually scored by an experienced electroencephalographer in random order, blinded to the point in time of the recording and blinded to the patient who the epoch belonged to. Each epoch was placed in one of the following categories: iso-electric, low voltage, burst suppression, diffuse slowing, normal, or epileptiform discharges. Each epoch could only be classified into one category and the reviewer was allowed to skip the epoch if it contained too many artifacts for a clear classification. Iso-electric epochs were defined as epochs without any visible EEG activity. Low voltage epochs were defined as epochs with EEG activity below 20 μV. Burst suppression was defined by the presence of clear increases in amplitude (bursts), followed by inter-burst intervals of at least 1 sec with low voltage activity (suppressions). Bursts were required to have EEG amplitudes higher than 20 μV, otherwise the epoch was categorized as low voltage. Diffuse slowing was defined as a continuous EEG pattern with a dominant frequency below 8 Hz. Epileptiform discharges included seizures and generalized periodic discharges (GPDs).

Somatosensory Evoked Potential

Daily SSEP measurements were performed during the first 5 days of the ICU stay or until discharge from the ICU. The SSEP was measured after electrical stimulation of the right and left median nerve using a bipolar surface electrode at the wrist. Stimulus duration was 0.3 msecs and stimulus amplitude was

adjusted until a visible twitch was produced. Two sets of >200 responses were averaged, band pass filtered between 0.1 Hz and 2.5 kHz, and notch filtered around 50 Hz. Stimulus frequency was set at 1.7 Hz. Silver-silverchloride cup electrodes were placed at the elbow, Erb's point, cervical spine (C5), and 2 cm posterior to C3 and C4 (C3' and C4'). Fz was used as a reference electrode. SSEP recordings were made using a Nicolet Bravo system (Viasys, Houten, the Netherlands).

Outcome assessment

Standard neurological examination was performed daily during the ICU stay. Follow-up was performed after 1, 3 and 6 months. The outcome assessment after 1, 3 and 6 months after resuscitation was always done by the same author (MCC). At 1 or 3 months, the CPC score was determined during a personal meeting, or based on a telephone call. The outcome assessment after six months was always based on a telephone call. The primary outcome measure was the best score within 6 months on the five point Glasgow-Pittsburgh Cerebral Performance Categories (CPC)[22]. Outcome was dichotomized between "good" and "poor". A "good" outcome was defined as a CPC score of 1 or 2 (no or moderate neurological disability), and a "poor" outcome as a CPC score of 3, 4, or 5 (severe disability, comatose or death).

Statistical Analysis

Collected baseline characteristics include age, sex, weight, location of cardiac arrest (in hospital versus out of hospital), cause of cardiac arrest and initial cardiac rhythm. Body temperature and drug registration during ICU stay were evaluated as well.

The following variables were compared between the groups of patients with a good neurological (CPC 1–2) outcome and poor neurological (CPC 3–5) outcome: Age, sex, percentage of out of hospital cardiac arrest, cause of cardiac arrest, initial rhythm, start time of EEG recording, duration of EEG recording and the maximum dose of sedative and analgesic drugs during the first 24 hrs after cardiac arrest. Statistical analysis was performed using a Pearson Chi-Square test or a Fisher's Exact test for the parameters that were categorical. A Pearson Chi-Square was used when no subgroup had an expected count less than 5, else a Fisher's Exact test was used. An independent *t*-test or a Mann-Whitney U test was applied when the parameters were continuous. A Mann-Whitney U test was performed in cases were the parameter was not normally distributed.

To evaluate the value of EEG in early prognostication, sensitivities, specificities, positive and negative predictive values, and their 95% confidence intervals (95% CI) were calculated for the different EEG patterns at 12 and 24 hrs after cardiac arrest. Those were compared to the sensitivity and specificity of absent short-latency (N20) SSEP responses within 24 hrs for predicting poor neurological outcome. Note that all mentioned time periods start at the time of cardiac arrest.

Results

Sixty consecutive patients were included in the study. Of these, four patients were excluded in a later stage, two because of intracerebral hemorrhages, one because of technical problems during the EEG registration and the last one because of death within the first hour of registration. None of the remaining 56 patients was lost during follow-up. Twenty-seven patients (48%) had a good neurological outcome (best CPC score within 6 months $\leq$2). Two of them died within the first month due to cardiac failure, and one suffered from a cerebral vascular accident after he recovered and was transferred to a nursing home. The other 24 patients with good neurological were all able to return to their homes and were still alive after 6 months. Poor outcome occurred in 29 patients, where one patient had severe neurological disabilities (CPC 3) before he died from cardiac failure; the remaining twenty-eight patients never regained consciousness (CPC 4–5) and died within the first month. An overview of the patient and measurement characteristics is given in Table 2.1.

SSEP during hypothermia

Bilateral absence of the cortical N20 SSEP response was present in seven patients within the first 24 hrs (Table 2.2A). All of them had a poor outcome and in none of them the N20 returned in later SSEP measurements. The sensitivity of bilateral absent N20 responses during hypothermia for predicting poor neurological outcome was 24% with a specificity of 100%. The negative predictive value of a bilateral absent SSEP was 55%, with positive predictive value of 100% (Table 2.3).

EEG patterns

An overview of the trends in EEG patterns in patients with poor and good neurological outcome is given in Figure 2.1. Some EEG epochs were excluded from analysis because of artifacts, this occurred in 4% of the epochs.

Table 2.1: Comparison between patient characteristics, measurement characteristics and sedation levels between the patients with good neurological outcome and poor neurological outcome.

	Poor neurological outcome (Cerebral Performance Category score 3–5)	Good neurological outcome (Cerebral Performance Category score 1–2)	*p*
Number of patients	29	27	
Number of male	21 (72%)	17 (63%)	.45
Age (yrs)	70 (std 12) (range: 44–86)	66 (std 11) (range: 45–88)	.17
Number of out-of-hospital cardiac arrest	23 (79%)	26 (96%)	.10
Initial Rhythm			.001
Ventricular fibrillation	17 (59%)	24 (89%)	
Asystole	6 (21%)	0 (0%)	
Bradycardia	5 (17%)	0 (0%)	
Unknown	1 (3%)	3 (11%)	
Presumed cause of cardiac arrest			.004
Cardiac	16 (55%)	25 (93%)	
Other origin	6(21%)	0 (0%)	
Unkown	7 (24%)	2 (7%)	
Start of EEG registration after cardiac arrest (hr)	6 (std 3) (range: 2–13)	7 (std 4) (range: 2–21)	.51
Duration of EEG registration (hrs)	54 (std 38) (range: 2–136)	75 (std 21) (range: 38–108)	.01
Patients sedated with propofol	28[a] (97%)	27[a] (100%)	1.00
Propofol dose (mg/hr/kg)	2.6 (std 1.1) (range: 1.0–6.2)	2.9 (std 0.9) (range: 0.2–4.8)	.33
Patients treated with fentanyl	17 (58%)	16 (59%)	.96
Fentanyl dose (μg/hr/kg)	1.7 (std 1.1) (range: 0.7–4.7)	1.9 (std 0.6) (range: 0.7–2.7)	.07
Patients treated with remifentanil	12 (41%)	12 (44%)	.82
Remifentanil dose (μg/hr/kg)	5.0 (std 3.2) (range: 1.9–13.3)	8.5 (std 4.7) (range: 2.5–14.7)	.07

[a] In contrast to the sedation protocol, one patient with poor neurological outcome was sedated with midazolam (37 μg/hr/kg) instead of propofol. In both groups two patients received midazolam (27.4–63.8 μg/hr/kg) additional to the sedation with propofol.

Within 12 hrs after resuscitation, 44% of the patients with good neurological outcome showed a continuous pattern, while at this stage none of the patients with poor neurological outcome showed a continuous pattern (Table 2.2B). Therefore, the presence of a continuous EEG pattern after 12 hrs could be used to reliably predict good neurological outcome (Table 2.3).

Table 2.2: Somatosensory evoked potential results and electroencephalogram patterns for patients 12 and 24 hrs after resuscitation.

	Time After Resuscitation (hrs)	Poor neurological outcome (Cerebral Performance Category score 3–5)	Good neurological outcome (Cerebral Performance Category score 1–2)
A: SSEP: bilateral absent N20 vs. present N20			
SSEP N20 absent	<24	7	0
SSEP N20 present	<24	22	27
B: EEG after 12 hrs: iso-electric, low voltage or burst suppression EEG vs. continuous EEG patterns[a]			
EEG iso-electric or low-voltage or burst suppression	12	26	13
EEG continuous	12	0	10
C: EEG after 24 hrs: iso-electric or low voltage EEG vs. burst suppression or continuous EEG patterns[b]			
EEG iso-electric or low-voltage	24	8	0
EEG burst suppression or continuous	24	12	26
D: EEG after 24 hrs: iso-electric, low voltage or burst suppression EEG vs. continuous EEG patterns[b]			
EEG iso-electric or low-voltage or burst suppression	24	19	1
EEG continuous	24	1	25

EEG, electroencephalogram; SSEP, somatosensory evoked potential.

[a] Three patients with poor neurological outcome were missing: one already died, two due to EEG artifacts. Four patients with good neurological were missing: two because the EEG registration was started after 12 hrs, two due to artifacts; [b] Nine patients with poor neurological outcome were missing: six already died, two due to artefacts and one due to logistical problems. One patient with good neurological was missing due to logistical problems.

Within 24 hrs after resuscitation, 40% of the patients with poor neurological outcome still showed an iso-electric or low-voltage EEG pattern, while none of the patients with good neurological outcome showed one of these patterns at this stage (Table 2.2C). The sensitivity of low voltage or iso-electric EEG patterns for predicting poor neurological outcome after 24 hrs was 40% with a specificity of 100% (Table 2.3). The negative predictive value was 68% and the positive predictive value 100%.

All patients with good neurological outcome, except one, (95%) showed improvement towards a continuous slowed pattern within 24 hrs after resuscitation (Table 2.2D). An example is shown in Figure 2.2. In contrast, all patients with poor neurological outcome, except one, (96%) showed burst suppression, low voltage, or iso-electric EEG patterns during the first 24 hrs after resuscita-

Table 2.3: Sensitivity, specificity and predictive values for early prediction of good and poor neurological outcome.

	Time after resusci-tation (hrs)	Predicting	Sensitivity (95% CI)	Specificity (95% CI)	Positive predicting value (95% CI)	Negative predicting value (95% CI)
Somatosensory evoked potential N20 absent	<24	Poor outcome	24 (10–44)	100 (87–100)	100 (59–100)	55 (40–60)
EEG continuous	12	Good outcome	43 (23–66)	100 (86–100)	100 (69–100)	67 (50–81)
EEG iso-electric or low-voltage	24	Poor outcome	40 (19–64)	100 (86–100)	100 (63–100)	68 (51–82)
EEG iso-electric low-voltage or burst suppression	24	Poor outcome	95 (75–100)	96 (80–100)	96 (80–100)	95 (75–100)

CI, Confidence interval; EEG, electroencephalogram.

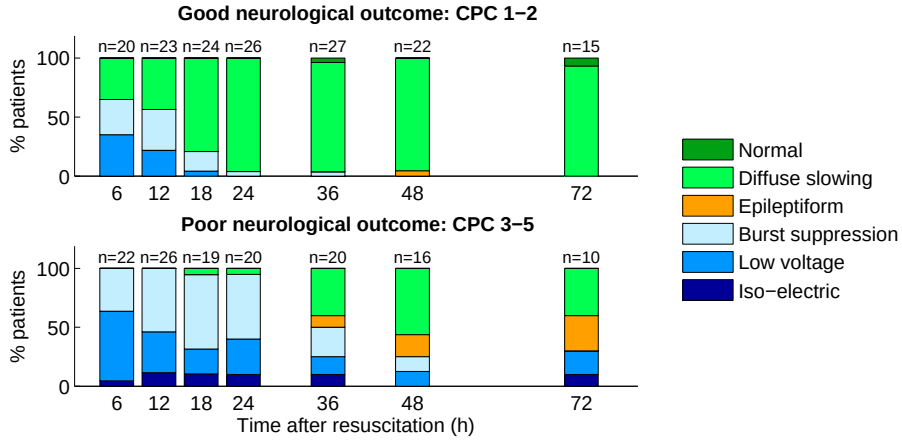

Figure 2.1: Trend in EEG patterns for patients with different neurological outcomes. Top: patients with good neurological outcome (Cerebral Performance Category [*CPC*] score 1–2). Bottom: patients with poor neurological outcome (3–5). In all patients with a continuous EEG pattern after 12 hrs (diffuse slowing or normal, top panel), outcome was good. In all patients with iso-electric or low voltage EEG after 24 hrs (bottom panel), outcome was poor. Burst-suppression at 24 hrs is also associated with poor outcome, but does not reach a specificity of 100%.

tion (Table 2.2D). In eight of them, the EEG improved to a continuous pattern in a later stage within 48 hrs. Six of those patients showed a low voltage

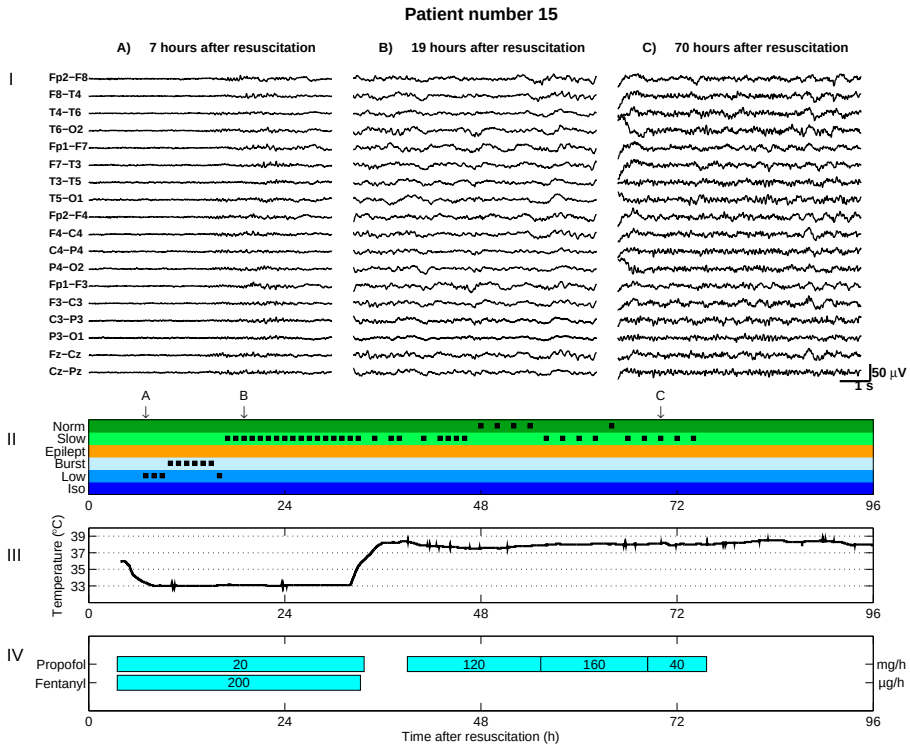

Figure 2.2: Example of the evolution of electroencephalogram (EEG) patterns of patient number 15 with a good neurological outcome (Cerebral Performance Category score 1). The EEG pattern is improving from a low voltage and burst suppression pattern to a diffuse slowed pattern before the end of the hypothermia period. From top to bottom: (I) Three examples of the EEG at different points in time to demonstrate the evolution of the EEG patterns over time. (II) Trend line of EEG pattern based on visual interpretation of 5 min epochs. (*Norm*, normal, *Slow*, diffuse slowed, *Epilept*, epileptiform discharges, *Burst*, burst suppression, *Low*, low voltage, *Iso*, iso-electric). (III) Body Temperature. (IV) Use of sedative and analgesic drugs. EEG, electroencephalogram

EEG in the beginning of the registration, and two patients showed a burst suppression pattern. A typical example is shown in Figure 2.3. In all other patients the EEG did not become continuous even after 72 hrs, for example patient 13 in Figure 2.4.

Table 2.3 summarizes the relevant sensitivity, specificity and predictive value rates of the different EEG patterns and SSEP responses for predicting for predicting good (CPC score 1–2) and poor outcome (CPC 3–5) within 24 hrs after resuscitation.

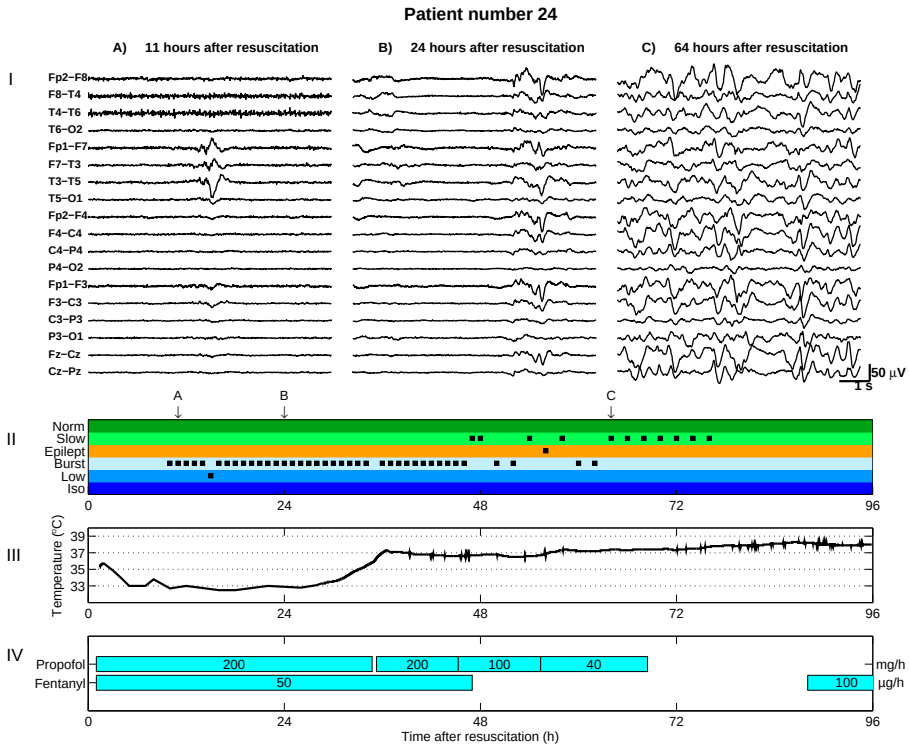

Figure 2.3: Trend in EEG of patient number 24 with poor neurological outcome (Cerebral Performance Category score 5). In this patient the EEG is improving from a burst suppression to a continuous, but diffuse slowed pattern, however not within the first 24 hrs. (*Norm*, normal, *Slow*, diffuse slowed, *Epilept*, epileptiform discharges, *Burst*, burst suppression, *Low*, low voltage, *Iso*, iso-electric).

Presence of epileptiform activity

In eight patients (14%) the EEG was classified as seizure activity or generalized periodic discharges. In seven patients the discharges continued for several hours and despite treatment with anti-epileptic drugs in five of them (phenytoin; in two cases levetiracetam was given additionally). All those seven patients had poor neurological outcome. In five of those patients the epileptiform discharges followed after a burst suppression pattern, the last two patients showed a continuous pattern before the GPDs occurred. One patient with generalized periodic discharges had a good outcome, in this patient the discharges were self-limiting within 2 hrs and anti-epileptic drugs were not given. This patient already showed a continuous pattern before the start of the generalized periodic discharges.

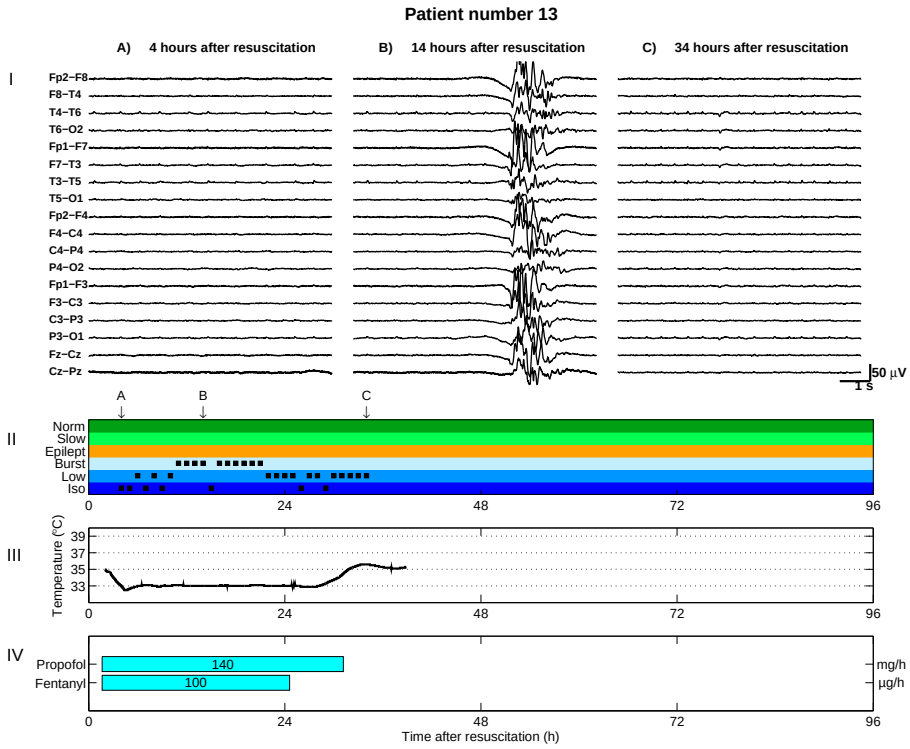

Figure 2.4: Trend in EEG of patient number 13 with poor neurological outcome (Cerebral Performance Category score 5). In this patient the EEG never improved to an EEG pattern better than burst suppression. (*Norm*, normal, *Slow*, diffuse slowed, *Epilept*, epileptiform discharges, *Burst*, burst suppression, *Low*, low voltage, *Iso*, iso-electric).

In four additional patients (7%) the EEG showed a burst suppression pattern, with the bursts consisting of sharp waves. In two patients, rhythmic movements of the eyes and mouth were present during the bursts, indicating a myoclonic status epilepticus. All these four patients had poor neurological outcome, despite treatment with phenytoin.

Three other patients with continuous, diffuse slowed EEG patterns showed minor epileptiform abnormalities. In one of them rhythmic activity of the feet, shoulder and eyes was present. All these three patients responded well to treatment with anti-epileptic drug and had good neurological outcome.

Discussion

In this study we explored the value of continuous EEG monitoring for the early prediction of neurological outcome in patients after cardiac arrest treated with hypothermia. In our study population, 27 out of 56 patients (48%) obtained good neurological outcome (CPC 1–2), which is within the 34%–55% range mentioned in other studies[1–4]. The first 24 hrs of EEG after resuscitation were the most useful in the prediction of, both good and poor neurological outcome.

Our SSEP findings are comparable to the work of Bouwes et al.[3]. In their study of 77 patients, bilateral absence of the cortical N20 responses of median nerve SSEP performed during mild hypothermia 24 hrs after resuscitation predicted a poor neurological outcome with a sensitivity of 27% and a specificity of 100%. However, in literature one patient treated with TH after cardiac arrest, with bilateral absent N20 responses at day 3 and with good neurological outcome (CPC 1) is described[9]. Despite this single case, pooled analysis of recent SSEP studies on hypothermia patients[3,9,10,16] gives a very low false positive rate of 1.2%[23,24].

After 12 hrs, 44% of the patients with good neurological outcome showed a continuous EEG pattern, while none of the patients with poor neurological outcome showed continuous EEG patterns. The evolution from absent cortical activity to an intermittent pattern and finally to a continuous pattern in patients with good neurological outcome was already described in 1984 by Jørgensen and Malchow-Møller[25–27]. They studied patients after cardiac arrest with no detectable cortical activity in the initial EEG. These patients were not treated with therapeutic hypothermia and were typically unsedated. In their study, patients with good neurological outcome and absent EEG activity measured directly after the cardiac arrest, showed a return of cortical activity within 10 mins to 8 hrs. In these patients the EEG activity could occur intermittently for as long as 16 hrs; thereafter the activity became continuous in all patients with good neurological outcome[25]. In contrast, patients with poor neurological outcome showed slower or no recovery in their EEG patterns[26,27].

The sensitivity for predicting poor outcome of low voltage and iso-electric EEG patterns 24 hrs after resuscitation was 40%, with a specificity of 100%. This is significantly larger than the SSEP at 24 which had a sensitivity of 24% and specificity of 100%. This difference in sensitivity most likely results from the larger vulnerability of cortical pyramidal cell synaptic function than the

thalamocortical (TC) synapses in ischemia: pyramidal cell synaptic function is mainly reflected by the EEG, while SSEP mainly evaluates the TC synaptic function[28].

A burst suppression pattern after 24 hrs was also associated with poor neurological outcome, however not at a specificity of 100%: the sensitivity was 95% and the specificity was 96%. In some patients with poor neurological outcome the burst suppression pattern improved to a continuous EEG pattern at a later stage. This illustrates that the time scale of improvement of the EEG pattern is a relevant factor in the prognosis. Further differentiation of burst suppression patterns may be relevant in predicting poor outcome, as large differences in the type of burst suppression patterns exist, including more specific patterns associated with a poor outcome[29]. This was however not explored further in this study.

Our findings support earlier studies in patients not treated with TH, which report that the combined group of iso-electric, low voltage and burst suppression EEG patterns is associated with poor neurological outcome[7,30]. More recently, in a study of Rundgren et al., 95 cardiac arrest patients treated with therapeutic hypothermia were studied with continuous EEG as well. In their study, a simplified 2 channel amplitude integrated EEG was used, which is more easy to apply in the ICU and shortens the time of visual interpretation[5,31]. Their study used a similar cooling regimen, except that some patients were cooled using intravenous instead of external cooling. Sedation levels with propofol during hypothermia were also similar to our study. It was shown that an initial flat pattern had no prognostic value while a continuous EEG pattern at the start of registration or at the beginning of normothermia was associated with good neurological outcome[5,31]. Our findings confirm these results. In addition, we also studied the EEG evolution over time, showing that the EEG patterns at 12 or at 24 hrs were more informative than the initial EEG and the EEG at normothermia (see Figure 2.1). A recent study of Rossetti et al.[10] also reported that “prolonged burst suppression” activity is associated with poor neurological outcome in patients treated with hypothermia. However, a detailed comparison between their and our findings is difficult, as not in all cases it is clear at which moment after CA their EEGs were evaluated. In addition, different sedatives were used in their study compared to ours (midazolam instead of propofol).

Epileptiform discharges or burst suppression patterns containing sharp waves or associated with epileptiform activity were present in 21% of the patients. All those epileptiform discharges were associated with poor outcome, except for one patient (with self-limiting epileptiform discharges). These findings are similar to other studies, which also concluded that both generalized periodic discharges and a status epilepticus are associated with poor outcome, but not invariably so[32–36]. The background EEG pattern prior to the development of the status epilepticus might have a prognostic value in these patients[5]. Minor epileptiform abnormalities on a continuous background EEG were present in three patients, those three patients responded to anti-epileptic drugs and recovered well.

In our study, we tried to identify early predictors during the first 24 hrs using ongoing EEG activity. Clinical scores, in particular the Glasgow coma score, were not used in this analysis, as these are highly unreliable during the first 24 hrs as patients were sedated and treated with therapeutic hypothermia. Furthermore we did not include initial rhythm, cause of cardiac arrest, location of cardiac arrest, comorbidities, or other scores such as the APACHE score in the statistical modeling. It is well known that any of these factors affects neurological recovery as well[4,37]. However, in this study we primarily focused on the predictive value of the EEG on its own, as the EEG directly reflects cortical neuronal function[17], known to be most sensitive to ischemic injuries.

Although all patients were treated with sedative drugs during the period of hypothermia according to the same treatment protocol, differences in sedation levels may have influenced the EEG patterns. However, no significant difference in sedation level between the group with good neurological outcome and poor neurological outcome was found (Table 2.1). We note however, that a trend was found in the dosages of fentanyl and remifentanil between the groups of patients with poor and good neurological outcome, with both drugs given in a higher dose in patients with good neurological outcome. Furthermore, it is unlikely that the most severe EEG patterns (iso-electric and low voltage) were caused by the use of propofol, fentanyl or remifentanil in the doses used, as the EEG is not suppressed at these doses, and typically only shows moderate slowing[38]. Other institutions may have different sedation regimens, which possibly could affect the EEG patterns. Therefore, it is presently unclear to what extent our results to patients treated with higher doses or different sedatives can be extrapolated.

A possible shortcoming of this study was that the treating physicians were not completely blinded to the EEG and SSEP results. This may have led to "self-fulfilling prophecies". According to current treatment guidelines, treatment was stopped if the N20 response was bilaterally absent at day three. Furthermore, some patients died within the first week after cardiac arrest for other reasons, for example due to a second cardiac arrest. We cannot exclude that complete neurological recovery could have occurred in these patients. Furthermore, it should be noted that this was a single center study which may have had an effect on the visual analysis of the EEGs. Given however that the categories were defined in a very clear manner, it is unlikely that the interpretation of the patterns were significantly biased. Another limitation might be that we only used 5 min epochs of EEG data every hour, instead of the complete registration. However, it is unlikely that this had a significant influence on our results, since the EEG patterns typically evolved over hours.

In closing, this study provides additional support for the relevance of EEG monitoring in the ICU in patients treated with TH. Clearly, future studies are needed, preferably multi-center studies, to confirm these results and to tighten the confidence intervals, in particular of the specificity. In addition, as visual analysis of EEG monitoring is time consuming and can only be done by experienced electroencephalographers, it will become crucial to use automatic classification techniques[39] or to only extract the most important quantitative EEG variables[40].

Conclusions

This prospective study show that EEG monitoring during the first 24 hrs after resuscitation can contribute in the prediction of both good and poor neurological outcome. For successful recovery, the time scale during which EEG improves towards a continuous pattern has to occur within the order of 24 hrs. In our study, an iso-electric or low voltage EEG pattern 24 hrs after resuscitation was associated with poor neurological outcome with a sensitivity that was almost two times larger than bilateral absence of the N20 SSEP response.

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Chapter 3

Burst-suppression with identical bursts: a distinct EEG pattern with poor outcome in postanoxic coma

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Abstract

Objective: To assess the incidence, prognostic significance, and quantified EEG characteristics of “burst-suppression with identical bursts” and to discuss potential pathophysiological mechanisms.

Methods: Burst-suppression EEGs were identified from a cohort of 101 comatose patients after cardiac arrest, and from our complete EEG database of 9600 EEGs, since 2005. Patterns with and without identical bursts were classified visually by two independent observers. Of patients after cardiac arrest, outcomes were assessed at three and six months. Identical and non-identical burst-suppression patterns were compared for quantified EEG characteristics, including cross-correlation of burstshapes, and clinical outcome. Quantitative analysis of burstshape was applied to the first 500ms of each burst.

Results: Of 9701 EEGs, 240 showed burst-suppression, 22 with identical bursts. Identical bursts were observed in twenty (20%) of 101 comatose patients after cardiac arrest between a median of 12 and 36 hours after the arrest, but not in the six patients with other pathology than cerebral ischemia, or the 183 with anesthesia induced burst suppression. Inter-observer agreement was 0.8 and disagreement always resulted from sampling error. Burst-suppression with identical bursts was always bilateral synchronous, amplitudes were higher (128 vs. 25 μV, $p=0.0001$) and correlation coefficients of burstshapes were higher (95% >0.75 vs. 0% >0.75, $p<0.0001$) than in burst-suppression without identical bursts. All twenty patients with identical bursts had a poor outcome versus 10 (36%) without identical bursts.

Conclusion: “Burst-suppression with identical bursts” is a distinct pathological EEG pattern, which in this series only occurred after diffuse cerebral ischemia and was invariably associated with poor outcome.

Significance: In comatose patients after cardiac arrest, “burst-suppression with identical bursts” predicts a poor outcome with a high specificity.

Introduction

Burst-suppression in the electroencephalogram (EEG) is characterized by high amplitude events (bursts) alternated by periods of low or absent activity (suppressions)[1,2]. This pattern can be physiological, for instance during early development, or pathological, for example in almost half of comatose patients within the first 48 hours after cardiac arrest[3]. Also, burst-suppression can be induced by anesthetics[4]. Under pathological conditions, it is usually associated with a poor prognosis. However, in a previous prospective cohort study, we found that 18% of patients with burst-suppression at 12 or 24 hours after cardiac arrest had a good functional outcome[3].

Characteristics to classify burst-suppression patterns into subgroups with presumed differences in clinical significance include the duration of the bursts and interburst intervals, maximum peak to peak voltage, area under the curve, and the ratio of power in high versus low frequencies[5]. For example, longer suppressions were associated with poorer recovery in patients with postanoxic coma[6]. Still, predictive values for poor outcome remain too low to allow treatment decisions.

Extreme similarity of burstshape is a distinct feature of some burst-suppression patterns. Herewith, subsequent bursts in a particular channel are almost "photographic" copies. Patterns with this particular characteristic have been sporadically reported and considered a rarity[7,8]. However, through standard use of continuous EEG in comatose patients on the intensive care, we have learned that these occur relatively frequent within the first days after acute diffuse cerebral ischemia.

Here we report on the incidence and prognostic significance of "burst-suppression with identical bursts" and quantify its EEG characteristics. We show that this is a distinct pathological EEG pattern that only occurs after diffuse cerebral ischemia and is invariably associated with a poor outcome in these patients. Since both morphology and clinical significance apparently differ from other burst-suppression patterns, we propose to label the pattern as "burst-suppression with identical bursts". We discuss potential pathophysiological mechanisms.

Methods

Burst-suppression EEGs

We identified EEGs with bursts-suppression in two ways. First, we took these from comatose patients after cardiac arrest that were included in a prospective cohort study on the predictive value of continuous EEG on outcome between June 1st 2010 and September 31st 2012. Design, eligibility criteria, and main outcomes of the first 60 patients included in this study have been published previously[3]. In brief, since June 1st 2010, consecutive adult comatose patients after cardiac arrest, treated with hypothermia, were included within twelve hours after the arrest to undergo continuous EEG monitoring on the intensive care unit. Monitoring continued until patients regained consciousness, died, or up to five days. For this study, the institutional review board waived the need for informed consent.

Second, we identified burst-suppression EEGs from the Medisch Spectrum Twente's, complete hospital database. Here, since January 2005, all EEGs are systematically categorized. Hence, EEGs that meet the criteria for burst-suppression are labeled as such. We took all EEGs from patients aged 18 years or older, recorded between January 2005 and December 2012 and labeled as "burst-suppression".

EEG recordings

For all recordings, electrodes were applied according to the international 10–20 system, using 19 channels. Electrode impedances were kept below 5 kΩ. Sampling frequency was set to 256 Hz. A Neurocenter EEG system (Clinical Science Systems, the Netherlands) was used with a TMS-i full band EEG amplifier (TMS international, the Netherlands) or a BrainLab EEG recording system (OSG BVBA, Belgium) was used. Data were stored to disk for off-line analysis.

Visual analysis of burst-suppression patterns

Burst-suppression was defined as any pattern with high amplitude events (>20 μV) alternated with periods of low (<10 μV) or absent EEG activity of at least one second. After visual identification of burst-suppression patterns, these were visually sub-classified into patterns with identical bursts and patterns without identical bursts. Bursts were considered identical, if the first 500 ms were identical, irrespective of amplitude or subsequent duration of bursts or inter-burst intervals.

Of comatose patients after cardiac arrest, this visual analysis was done independently by two investigators (MT-C, MvP) in automatically selected epochs of five minutes at 12 and 24 hours after cardiac arrest. These investigators were blinded for the patients' clinical condition during the registration, the recording time of the epoch, and the patient's outcome. In case of disagreement, the final classification was decided by consensus in consultation with a third observer (JH), who had access to the complete recordings, but was blinded for the patients' outcome. All EEG analyses were done after the registrations and EEG played no role in initial treatment decisions. All other burst-suppression EEGs from the hospital data base were reviewed by a single observer (MvP), blinded for the underlying condition and the patient's outcome.

Quantitative analysis of burst-suppression patterns

Quantitative analysis of correlation between shapes of subsequent bursts, burst amplitudes, and durations of the interburst intervals was done for EEGs from comatose patients after cardiac arrest. For this purpose, the initiation of 50 subsequent bursts was annotated manually in a particular bipolar channel in each EEG. This was typically done at twelve or 24 hours after the arrest. Correlations between the burstshapes (truncated to a duration of M=127 samples i.e. 500 ms) were calculated using the cross-correlation over a range of lags (from –maxlag to maxlag, with maxlag=M–1). Subsequently, the maximum value of the 2*maxlag+1 values was determined. This resulted in 1225 different correlations for each patient, from which the mean correlation coefficient per patient was determined. In addition, the mean and maximum amplitude of the first 500 ms of the 50 bursts were calculated. Inter-burst intervals were defined by the time difference between the initiation of bursts. All routines were implemented in Matlab.

Treatment

Comatose patients after cardiac arrest were treated according to current standard therapy, as described previously[3]. In short, hypothermia of 33°C was induced as soon as possible after the arrest and maintained for 24 hours by intravenously administered cold saline and cooling pads. Propofol was used for sedation to a level of −4 or −5 at the Richmond Agitation Sedation Scale and discontinued after normothermia had been reached, if possible. Fentanyl or Remifentanil was used against shivering. Of patients other than those included in the prospective cohort study, medication during the registration was not prospectively collected.

Outcome assessment

Of comatose patients after cardiac arrest, that had been included in our prospective cohort study, outcome assessment was done at three and six months by telephone (MT-C). The primary outcome measure was the best score on the Cerebral Performance Category (CPC) within six months dichotomized between "good" (CPC 1 or 2) and "poor" (CPC 3, 4, or 5). Secondary outcome measures included mortality[3]. Of patients other than those included in the prospective cohort study, outcome was not prospectively assessed.

Statistical analysis

From all patients with burst-suppression EEGs, the proportions of burst-suppression patterns with and without identical bursts were calculated for each underlying condition. All further analyses were done for the subgroup of patients that had been included in our cohort study on the diagnostic value of continuous EEG in comatose patients after cardiac arrest. Inter-observer agreement for the appointment of "identical bursts" between the two independent observers was analyzed with Cohen's Kappa. Identical burst-suppression patterns were compared with other burst-suppression patterns with regard to clinical outcome and quantitative EEG characteristics (bilateral synchrony, amplitude, duration of inter-burst intervals, and correlation of burstshapes). Data are presented as proportions, or means ± standard deviations (SD). Between-group differences were analyzed with Fisher's exact or Student's *t*-test, if appropriate. For burst-suppression with or without identical bursts, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the prediction of poor outcome were calculated, including corresponding 95% confidence intervals (CIs).

Results

Incidence of burst-suppression with identical bursts

From our cohort of 101 comatose patients after cardiac arrest, 48 (48%) had burst-suppression patterns at twelve or 24 hours. Twenty (20%) had burst-suppression with identical bursts on visual analysis. Of all other 9600 EEGs in our database, 192 showed burst-suppression. Underlying conditions varied. Two had diffuse cerebral ischemia from other causes than cardiac arrest, both with identical bursts. Burst-suppression with identical bursts was not seen in the six patients with other pathology than cerebral ischemia, or in the 183 patients under anesthesia (Table 3.1). Three examples of burst-suppression without identical bursts are shown in Figure 3.1, and three examples of burst-suppression with identical bursts in Figure 3.2.

Table 3.1: Causes of burst-suppression patterns with and without identical bursts.

Cause of burst-suppression	Identical bursts	
	Yes	No
Cerebral ischemia		
Coma after cardiac arrest	20	28
Drowning	1	
Hanging	1	
Cerebral infarction		1
Other causes		
Traumatic brain injury		3
Therapeutic hypothermia		1
Propofol or sevoflurane anesthesia		183
Meningitis		1
Craniotomy		1
Total	22	218

Timing of burst-suppression with identical bursts

Baseline characteristics of comatose patients after cardiac arrest with burst suppression are summarized in Table 3.2. In these patients, burst-suppression with identical bursts was observed between a median of 12 (range 3–23) and 36 (range 15–53) hours after the arrest. These patterns were followed by burst-suppression without identical bursts in twelve patients (60%, subsequently low voltage in four), generalized periodic discharges in four (20%), epileptic discharges in one (5%), and low voltage in one (5%). In two patients, burst-suppression with identical burst was present up to death. Burst-suppression without identical bursts disappeared more gradually after approximately median 32 (range 17–72) hours after cardiac arrest. This pattern was followed by continuous slowing in 22 patients (79%, subsequently generalized periodic discharges in seven), generalized periodic discharges is three (11%), and low voltage in one (4%). In one patient, burst-suppression without identical burst was present up to death.

Inter-observer agreement

Cohen's Kappa for inter-observer agreement of identical vs. non-identical bursts was 0.8. Disagreement always resulted from selection of the observed epoch: either the inter-burst interval was longer than five minutes, so that bursts fell outside the epoch, or bursts were only partly represented within the epoch. Consensus was always readily reached by looking outside the epoch.

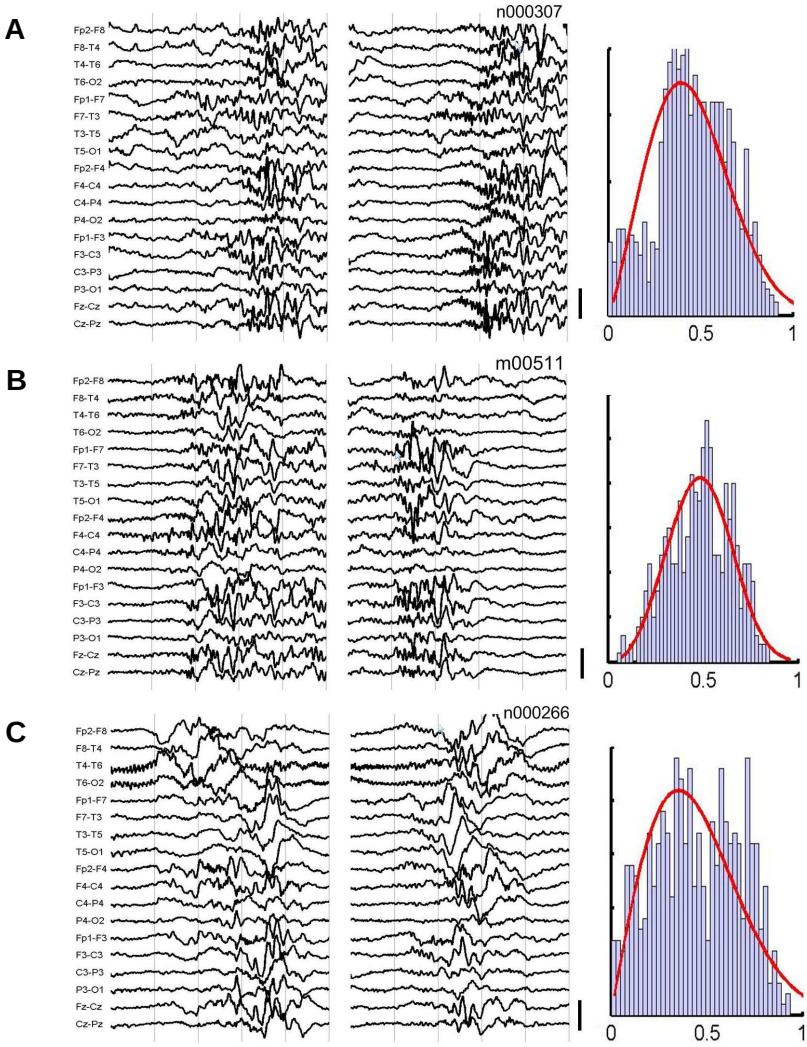

Figure 3.1: Left panels: illustration of EEGs of three comatose patients after cardiac arrest (A-C) showing "common" burst-suppression, without identical bursts. These patients were sedated with propofol 1 to 2.5 mg/kg/h. The individual EEG epochs have a duration 5 s. The mean interburst interval is 5.0 s (A), 9.8 s (B), or 11.8 s (C). Vertical bar: 100 μV. Filter settings 0.5-25 Hz. Right panels: histograms of correlation coefficients of burst-shape (r): in all three patients $r<0.75$.

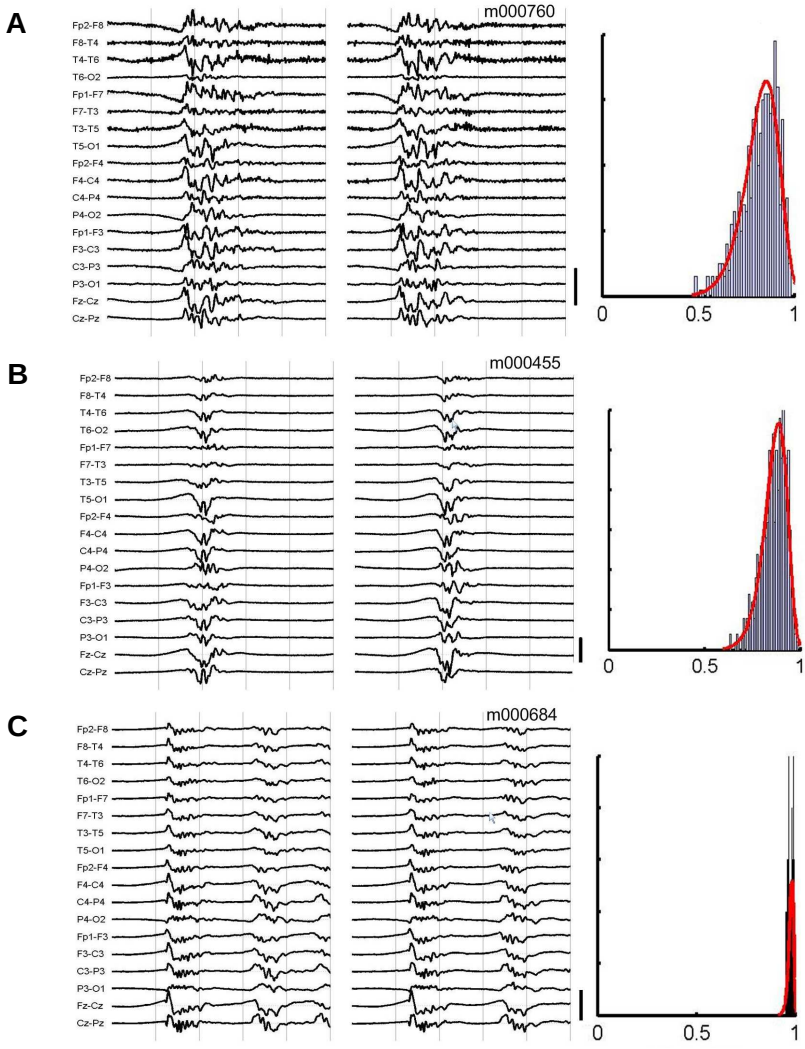

Figure 3.2: Left panels: illustration of EEGs of three comatose patients after cardiac arrest (A-C) showing "burst-suppression with identical bursts". A: recording from an eighty years old patient sedated with propofol 1 to 2.5 mg/kg/h; inter-burst interval 19 ± 9 s. B: 80 years old patient sedated with propofol 1 to 2.5 mg/kg/h; inter-burst interval 65 ± 64 s. C: 68 years old patient without sedative medication at normothermia. inter-burst interval 60 ± 23 s. The correlation extends over more than three seconds. The individual EEG epochs have a duration of 5.0 s. Vertical bar: 100 μV. Filter settings 0.5–25 Hz. Right panels: histograms of correlation coefficients of burst-shape (r): in all three patients r>0.85.

Table 3.2: Baseline characteristics of comatose patients after cardiac arrest with burst-suppression EEG with and without identical bursts.

	Identical bursts		
	Yes (n=20)	No (n=28)	*p* value
Age (years)	67	65	0.8
OHCA	17 (85%)	25 (89%)	0.7
Presumed cause of cardiac arrest			0.1
Cardiac	10 (50%)	20 (71%)	
Other	6 (30%)	2 (7%)	
Unknown	4 (20%)	6 (22%)	
Initial rhythm			0.02
VF	8 (40%)	21(75%)	
Asystole	8 (40%)	2 (7%)	
Bradicardia	3 (15%)	2 (7%)	
Unknown	1 (5%)	3 (11%)	
Propofol treatment	19 (95%)	28 (100%)	0.4
Propofol dosage (mg/kg/h)	2.5 ± 1.2	3.2 ± 1.2	0.05
Midazolam treatment	2 (10%)	6 (21%)	0.4
Midazolam dosage (μg/kg/h)	4.1 ± 12.6	11.9 ± 26.4	0.2
Fentanyl treatment	10 (50%)	24 (86%)	0.01
Fentanyl dosage (μg/kg/h)	0.9 ± 1.2	1.4 ± 0.8	0.06
Remifentanil treatment	10 (50%)	5 (18%)	0.03
Remifentanil dosage (μg/kg/h)	3.9 ± 2.2	5.2 ± 3.9	0.4

OHCA indicates out of hospital cardiac arrest; VF, ventricular fibrillation; dosage, maximum dosage within the first 24 hours.

Quantitative analysis

Quantitative EEG characteristics of comatose patients after cardiac arrest with burst-suppression with and without identical bursts are illustrated in Figures 3.1 and 3.2 and summarized in Table 3.3. Burst-suppression with identical bursts was more often bilateral synchronous than burst-suppression without identical bursts, amplitudes were higher, and correlation coefficients of burstshapes were higher. The only patient with identical bursts according to visual analysis, who still had a correlation coefficient lower than 0.75, had identical bursts of very short duration (~200 ms). In this patient, the time interval in which correlation was determined (500 ms) was probably too long to adequately measure correlation coefficients between the bursts. Although quantitative analysis was restricted to the first 500 ms, visual analysis revealed identical burstshapes extending beyond 500ms, in bursts with durations longer than 500ms. In burst-suppression with identical bursts, the interburst-intervals were invariably flat and all transitions between bursts and interburst-intervals were abrupt.

Table 3.3: Characteristics of (patients with) burst-suppression with and without identical bursts.

	Identical bursts on visual analysis		
	Yes (n=20)	No (n=28)	*p* value
Mortality	20 (100%)	10 (36%)	<0.0001
Bilateral synchrony	20 (100%)	18 (64%)	0.03
Mean amplitude (μV)	26.4 ± 16.0	6.5 ± 3.8	<0.0001
Maximal amplitude (μV)	127.8 ± 104.5	24.9 ± 14.2	0.0001
Mean inter-burst intervals (s)	53 ± 58	76 ± 339	0.8
Mean correlation coefficient of burstshape	0.85 ± 0.08	0.49 ± 0.08	<0.0001
Correlation coefficient of burstshape > 0.75	19	0	<0.0001

In number (%) of patients or mean ± standard deviation. Amplitude indicates amplitude in the first 500 ms of the burst.

Table 3.4: Sensitivity, specificity, and predictive values of burst-suppression with or without identical bursts within 48 hours after cardiac arrest for prediction of poor outcome.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Burst-suppression with identical bursts	40% (27%–55%)	100% (91%–100%)	100% (80%–100%)	63% (51%–73%)
Burst-suppression without identical bursts	20% (11%–34%)	65% (50%–77%)	36% (20%–56%)	45% (34%–57%)

Burst-suppression with or without identical bursts has been identified visually; 95% CI indicates 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Outcome

All twenty patients with identical bursts (100%) had a poor outcome vs. ten (36%) without identical bursts. Patients with a poor outcome never regained consciousness and all died. Sensitivity, specificity, PPV, and NPV of burst-suppression with and without identical bursts based on visual analysis for prediction of poor outcome are given in Table 3.4.

Discussion

We report on a distinct EEG burst-suppression pattern, which we propose to label “burst-suppression with identical bursts”. This pattern was present in twenty percent of our patients after diffuse cerebral ischemia, but was not seen in the six patients with other pathology than cerebral ischemia, or in the 183 patients under anesthesia. In burst-suppression with identical bursts, burst-shapes are highly similar and bilateral synchronous. Inter-burst intervals are variable in duration and invariably flat. Inter-observer agreement of identical vs. non-identical bursts was high (κ=0.8), and disagreement always resulted

from sampling error. All patients with burst-suppression with identical bursts, but not all patients with other burst-suppression patterns, died. This indicates that burst-suppression with identical bursts represents irreversible ischemic network damage of the brain predicting poor outcome with a specificity and PPV of 100%.

Burst-suppression patterns are characterized by oscillations with two time scales: a fast time scale for the intra-burst oscillations and a slow time scale for the periods between the bursts[8,9]. The burst initiation and termination are the result of bifurcations in the system: a bifurcation of an equilibrium attractor, resulting in a transition from resting to bursting, followed by a bifurcation from a limit cycle attractor back to the resting state[8,9]. During the bursting, with fast time-scale activity, there must also be a relatively slow process making neurons inexcitable[8].

In most situations, these two time scales result from processes involving fast and slow ion currents. An example is the slow activation of the Ca^{2+} dependent K^+ after-hyperpolarizing current (IAHP). This current is activated during bursting (fast time scale), as the intracellular Ca^{2+} concentration increases, and eventually results in ending of the burst. Hereafter, the intracellular Ca^{2+} is slowly removed and bursting may start again, as the outward K^+ current deactivates. Other scenarios include a calcium mediated inactivation of an inward current and voltage gated inactivation of inward, or activation of outward currents. These and other mechanisms are discussed in more detail in Izhikevich et al.[9]. Although such processes may result in identical burst morphology in single neurons, it is not straightforward how identical bursts arise at the spatial scale of an EEG.

Ching et al. proposed unifying mechanisms for all burst suppression patterns: an imbalance of neural activity and available energy[10]. However, both our observed burst phenomenology and the assumed pathophysiology of underlying conditions argue against the same mechanism for burst-suppression patterns from different causes. With regard to burst phenomenology, Ching's simulations generated variable bursts with equal (physiological) spectral content as in baseline EEG, with preservation of dominant power in the α frequency band. Otherwise, the spectral contents of our EEGs with "burst suppression with identical bursts" consist of frequencies ranging from the δ to β band, without a clear dominant frequency. Therefore, their claim that their model

is consistent with descriptions of burst-suppression in ischemic brain injury is not substantiated by our findings.

With regard to pathophysiology, the initial event in cerebral ischemia is synaptic failure[11,12] where excitatory synapses are more vulnerable than inhibitory[13]. As energy levels further decrease, Na^+/K^+ pumps will fail and neurons will depolarize[14–16]. In contrast, during medication induced burst-suppression, neurons have been shown to hyperpolarize[2], which has been ascribed to depression of glutamate mediated excitatory post-synaptic currents[17]. Furthermore, identical bursts in burst suppression typically occurred one to two days after the cardiac arrest, and continued during hours up to days. Since blood flow has been restored at this time, an absolute lack of energy is unlikely.

Burst-suppression with identical bursts suggests a deterministic process of burst generation, whereas other burst-suppression patterns rather depend on stochastic processes. In a previous report, we have shown that bursts-suppression with identical bursts represents a low dimensional state[8]. In patients after diffuse cerebral ischemia, selective synaptic failure is a candidate mechanism for this condition, since during cerebral ischemia synaptic function fails before the occurrence of membrane depolarization[12]. This may result in deterministic network behavior of the brain, especially since gap junctions are expected to be preserved[18]. Synaptic disturbances are presumably irreversible after relatively severe ischemia, which may explain the high case fatality rate of patients with burst-suppression with identical bursts[11,12]. Imaging techniques, such as MRI, may not detect such irreversible network damage, as synaptic changes need not to be accompanied by cell swelling[11,12], which is supported by the finding that approximately 20% of patients with a poor neurological outcome after diffuse cerebral ischemia had no abnormalities on early MRI[19].

Burst-suppression has been associated with poor neurological outcome of survivors of cardiac arrest before. However, in previous studies, predictive values were much lower than 100%[3,20–22]. In these studies, patterns were probably heterogeneous, including burst-suppression with and without identical bursts, supporting the notion of identical bursts being a distinct characteristic. Furthermore, the current study confirms our previous results with regard to timing: specific EEG changes only have a high predictive value if measured soon after cardiac arrest[3]. After a median of 36 hours, burst-suppression with identical bursts evolves into less specific pathological patterns.

Differences in baseline characteristics of patients with and without identical bursts include the initial rhythm before resuscitation, propofol dosages, and proportions of patients treated with fentanyl or remifentanil. Ventricular fibrillation occurred more often in patients with identical bursts. This is inconsistent with our finding of poorer outcome in patients with as compared with those without identical bursts, since ventricular fibrillation is associated with a better outcome after resuscitation as compared with asystole or bradycardia[23]. The lower dosages of propofol and the smaller proportions of patients treated with fentanyl or remifentanil in patients with as compared to those without identical bursts probably reflects more severe ischemic cerebral damage, in which less sedative medication was needed during ventilation and hypothermia.

Our study has certain limitations. First, some comatose patients after cardiac arrest did not die as a result of cerebral damage, but from other complications. It cannot be excluded that neurological recovery would have occurred in these patients. Second, it was a single center study, which may have influenced treatment decisions or EEG analysis. Third, most recordings of burst-suppression with identical bursts after cardiac arrest were during treatment with propofol. However, the observed identical burst-suppression patterns cannot be solely caused by this drug. Propofol induced EEG changes are well known. In the relatively low dosages that were used in our patients, the EEG remains continuous, with anteriorization of the "alpha" rhythm[24]. If burst-suppression is induced by propofol, bursts are heterogeneous and appear and disappear gradually[25,26], whereas our identical burst-suppression patterns were all characterized by abrupt transitions between bursts and suppressions. Moreover, several of our patients with burst-suppression with identical bursts were not medically sedated and two previously reported patients were neither treated with any sedative medication[7]. Fourth, data on EEG reactivity, brainstem reflexes, and clinically overt myoclonia were not collected prospectively, and retrospective collection appeared unreliable. Therefore this information is lacking.

Conclusion

Burst-suppression with identical bursts is a distinct pathological EEG pattern that in our series only occurred after diffuse cerebral ischemia. In comatose patients after cardiac arrest it was invariably associated with poor outcome.

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Chapter 4

EEG predicts outcome in patients with postanoxic coma during mild therapeutic hypothermia

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Submitted

Abstract

Objective: To assess the value of continuous EEG for prediction of outcome of comatose patients after cardiac arrest treated with mild therapeutic hypothermia (MTH).

Methods: In a prospective cohort study, we included subsequent patients with postanoxic encephalopathy after cardiac arrest, all treated with MTH. Continuous EEG was recorded during the first five days of ICU admission. Visual classification of EEG patterns was performed in 5 minute epochs at 12 and 24 hours after cardiac arrest by two observers independently, blinded for patients' conditions and outcomes. Patterns were classified as iso-electric, low-voltage, epileptiform, burst-suppression, diffusely slowed, or normal. Burst-suppression was subdivided into patterns with and without identical bursts. Primary outcome measure was the neurological outcome based on each patient's best achieved Cerebral Performance Category (CPC) score within 6 months after inclusion.

Results:One-hundred-forty-eight patients were included, 68 (46%) had favorable outcome (CPC 1–2). In patients with favorable outcome, EEG patterns improved within 24 hours after cardiac arrest, mostly towards diffusely slowed or normal. At 24 hours after cardiac arrest, the combined group of iso-electric, low voltage, and "burst-suppression with identical bursts" was invariably associated with poor outcome (sensitivity 48%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 66%). At 12 hours, normal or diffusely slowed EEG patterns were strongly associated with good outcome (sensitivity 56%, specificity 96%, PPV 93%, NPV 67%). Conclusions: EEG monitoring allows reliable prediction of both good and poor neurological outcome of postanoxic encephalopathy in patients treated with MTH within 24 hours after cardiac arrest.

Introduction

More than half of all comatose patients who have suffered from cardiac arrest never recover of unconsciousness as a result of postanoxic encephalopathy[1,2]. Early and reliable prediction of outcome in these patients may be helpful in clinical decision making and preventing continuation of unsuitable medical treatment. Predictive values of clinical measures and biochemical markers have become uncertain since the widespread introduction of mild therapeutic hypothermia (MTH)[3–8]. A bilateral absent cortical somatosensory evoked potential (SSEP) is considered to be the most reliable predictor of poor outcome[9,10]. However, its sensitivity is low, and neurological outcome remains uncertain in patients with preserved cortical SSEP responses.

The electroencephalogram (EEG) depicts a direct measurement of spontaneous brain activity. Previous studies have shown that EEG monitoring may be helpful in predicting early outcome in patients after cardiac arrest, treated with MTH[4,11–13]. We recently demonstrated that iso-electric and low-voltage EEG patterns at 24 hours after cardiac arrest were invariably associated with poor outcome, while normal or diffusely slowed patterns at 12 hours always predicted favorable outcome[12]. In addition, we recently discovered a distinct type of burst-suppression EEG, characterized by similar shapes of subsequent bursts. We labeled this pattern as “burst-suppression with identical bursts” and found that this pattern exclusively occurred in patients with diffuse cerebral ischemia and is invariably associated with poor outcome[14].

To confirm and extend the predictive value of EEG monitoring for both favorable and unfavorable neurological outcome of cardiac arrest patients, treated with MTH, we conducted a prospective multicenter cohort study.

Materials and Methods

Design

This prospective cohort study was conducted in intensive care units (ICUs) of two large teaching hospitals in the Netherlands. In the Medisch Spectrum Twente (Enschede), patients were included from June 2010 to April 2013. In the Rijnstate Hospital (Arnhem), patients were included from June 2012 to April 2013. The Medical Ethical Committee Twente waived the need for informed consent for EEG monitoring during ICU stay, as well as for follow-up by telephone consultation. A part of the results from the first 56 patients, included between June 2010 and July 2011, was reported previously[12].

Patients

Cardiac arrest patients with restoration of circulation and need for mechanical ventilation were admitted to the ICU for further treatment. Those who were comatose (Glasgow Coma Scale ≤8) at presentation in the emergency room and subsequently treated with MTH, were eligible for inclusion. Exclusion criteria were other neurological injuries, such as stroke or traumatic brain injury, or any known history of neurological disorder.

Treatment protocol

All patients were treated according to standard protocols for comatose patients after cardiac arrest. MTH, targeted at 33°C, was induced as soon as possible after arrival in the ICU and was maintained for 24 hours. Induction of MTH was performed by administering of 2 liters of cold saline intravenously and the use of cooling pads (Arctic Sun, Temperature management system, Medivance Inc. Louisville CO, USA) or a cooling matrass (Blanketrol II, Cincinnati Sub-Zero Medical Division, USA). Thereafter, patients were rewarmed to normothermia with a controlled speed of 0.25°C or 0.5°C per hour. In Medisch Spectrum Twente, propofol and fentanyl/remifentanil were used for sedation, and in most cases discontinued when body temperature had reached 36.5°C. In Rijnstate Hospital, patients received a combination of propofol, midazolam, and/or morphine. In both hospitals, a non-depolarizing muscle relaxant (rocuronium or atracurium) was added in case of severe compensatory shivering.

EEG recordings

In all patients, continuous EEG was recorded, starting as soon as possible after patient's arrival in the ICU and was continued for at least 3 days, or until discharge from the ICU. Twenty-one silver-silverchloride cup electrodes were placed on the scalp according to the international 10–20 system. Recordings were made using a Neurocenter EEG recording system (Clinical Science Systems, The Netherlands) or a Nihon Kohden system (VCM Medical, the Netherlands). EEG data during MTH played no role in actual prediction of outcome or treatment decisions. However, treating physicians were not blinded for the EEG and treatment of epileptiform discharges was allowed and left to the discretion of the treating physician.

All EEG analyses were performed after the registrations. Epochs of 5 minutes were automatically selected by a dedicated computer algorithm[15] at 12 and

24 hours after the estimated time of cardiac arrest. These time intervals were chosen based on the results of our previous study[12]. Epochs were visually scored by two reviewers (MT-C and MvP) independently. Visual analysis of the epochs was done in random order, blinded to the point in time of the epoch, the patient's clinical status during the recording, and outcome. EEG epochs were classified as isoelectric, low-voltage (<20 μV), epileptiform (including evolving seizures and generalized periodic discharges), burst-suppression, diffusely slowed, or normal. Diffuse slowing was defined as a continuous EEG pattern with a dominant frequency <8 Hz[12]. Normal EEG was defined as a continuous EEG pattern with a dominant frequency ≥8 Hz. Reactivity and anterior-posterior differentiation were not included in the definition of a normal EEG pattern. Burst-suppression was defined by the presence of a clear increase in amplitude (bursts), followed by interburst intervals of at least one second with low-voltage or absent activity (suppressions, <10 μV)). Burst-suppression patterns were subdivided into patterns with and without identical bursts[14]. "Burst-suppression with identical bursts" is defined as burst-suppression in which shapes of subsequent bursts are similar. The reviewer was allowed to skip the epoch if, mainly due to artifacts, no clear classification was possible.

Outcome

Primary outcome measure was neurological outcome expressed as the best score within 6 months after cardiac arrest on the five-point Glasgow-Pittsburgh Cerebral Performance Category (CPC)[16]. Outcome was dichotomized between "good" and "poor". Good outcome was defined as a CPC score of 1 or 2 (none or moderate neurological disability), and poor outcome as a CPC score of 3, 4, or 5 (severe disability, comatose, or death). CPC scores were determined at 3 and 6 months after cardiac arrest by a single investigator (MT-C) based on consultation by telephone. Neurological examination was performed daily during the ICU stay.

Statistical analysis

Patient characteristics and drug intake are presented in a descriptive way. Differences between groups of patients with good and poor neurological outcome were compared. Categorical variables were analyzed using Pearson's chi-square (if no subgroup had an expected count <5) or Fisher's exact test. Statistical analysis of differences between groups of continuous variables was performed using an independent *t*-test, after confirmation of a normal distribution of these values.

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of (groups of) specific EEG patterns for prediction of good or poor outcome after 12 or 24 hours after cardiac arrest were calculated, including the corresponding 95% confidence intervals (CI).

Results

One-hundred-fifty-four patients were included and continuous EEG monitoring was started at a mean of 10.6 (SD: 10.1) hours after cardiac arrest. Six patients were excluded in a later stage. Two patients were excluded because of intracerebral hemorrhage, one because of discontinuation of MTH after 5 hours, one because of technical problems of the EEG registration and two because they died within 12 hours, before any epochs for analysis could be selected. Of the remaining 148 patients, none were lost to follow-up. Hundred-and-fourteen were included in Medisch Spectrum Twente, and 34 in Rijnstate Hospital. Sixty-eight patients (46%) had good neurological outcome. A flowchart is shown in Figure 4.1, patient characteristics and the use of sedative or analgesic drugs are given in Table 4.1. EEG analysis could be performed in 98 patients at 12 hours, and in 129 patients at 24 hours after cardiac arrest. Analysis of other EEG epochs was not possible, because of artifacts or because EEG registration started after 12 hours after cardiac arrest.

EEG patterns in poor outcome

Of patients with poor neurological outcome, EEGs at 12 hours after cardiac arrest, showed iso-electric (n=10, 21%), low voltage (n=13, 27%), or burst suppression patterns with (n=11, 23%) or without (n=10, 21%) identical bursts. Two patients (4%) with poor outcome had epileptiform discharges at 12 hours after cardiac arrest, and two other (4%) had a continuous, diffusely slowed EEG. At 24 hours after cardiac arrest, the EEG of patients with poor neurological outcome had not improved in a substantial proportion: iso-electric (n=4, 6%), low voltage (n=9, 14%), or burst suppression pattern with (n=18, 28%) or without (n=18, 28%) identical bursts. Four patients with poor neurological outcome (6%) had epileptiform discharges at 24 hours. Eleven patients (17%) with poor neurological outcome showed a continuous, diffusely slowed EEG pattern at 24 hours after cardiac arrest. At later time points, more patients (41%) with a poor outcome, showed a continuous EEG pattern.

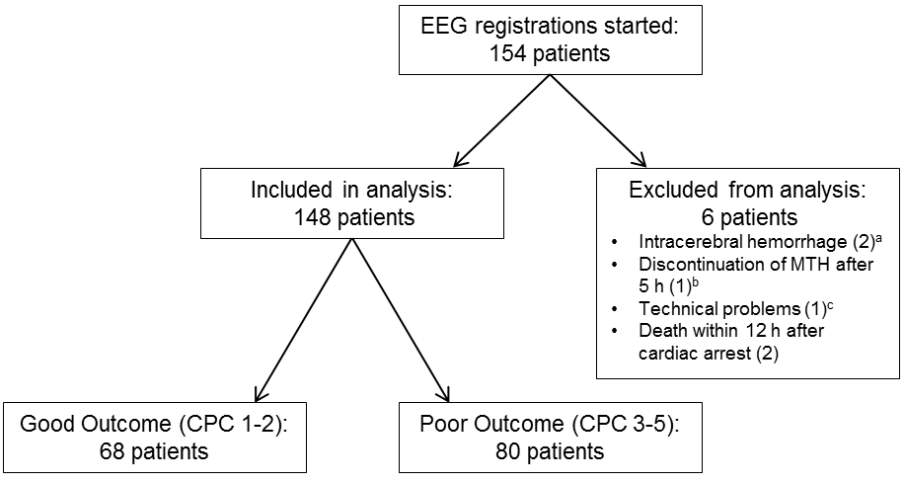

Figure 4.1: Flowchart of patients through this study.
[a] Both patients had poor outcome, one of them had a burst-suppression EEG with identical bursts both after 12 and after 24 hours after cardiac arrest, from the other patient no artifact free EEG data was available at 12 and 24 hours.
[b] This patient had poor neurological outcome, the EEG showed epileptiform discharges at 24 hours after cardiac arrest.
[c] This patient had good neurological outcome and showed a diffusely slowed EEG pattern at both 12 and 24 hours after cardiac arrest. The patient was excluded because the raw EEG data was not saved, and visual analysis of the EEG was done unblinded.

EEG patterns in good outcome

Patients with good neurological outcome had burst suppression patterns without identical bursts (n=19, 38%), diffusely slowed (n=18, 36%) or normal EEG patterns (n=10, 20%) at 12 hours after cardiac arrest. Three patients (6%) with good neurological outcome had a low voltage pattern at 12 hours after cardiac arrest. At 24 hours after cardiac arrest, the EEG of 56 (86%) patients with a good neurological outcome had improved towards a continuous pattern, either diffusely slowed (n=40, 62%) or normal (n=16, 25%). Only nine patients (14%) with good neurological outcome still showed a burst suppression pattern without identical bursts. Those nine patients showed improvement towards a continuous EEG pattern in a later stage.

An overview of the EEG patterns at 12 and 24 hours after cardiac arrest in patients with poor and good neurological outcome is given in Figure 4.2. Figure 4.3 represents illustrations of a burst-suppression pattern without and with identical bursts.

Table 4.1: Baseline characteristics of patients with good and poor neurological outcome.

	Poor neurological outcome (CPC 3–5)	Good neurological outcome (CPC 1–2)	*p*-value
Number of patients	80	68	-
Number of male	58 (73%)	47 (69%)	0.65
Age (years)	67 (std 12) (range: 27 to 82)	61 (std 12) (range: 34 to 93)	0.005
Number of OHCA	67 (84%)	64 (94%)	0.05
Initial Rhythm			<0.001
VF	39 (49%)	61 (90%)	
Asystole	27 (34%)	0 (0%)	
Bradycardia	6 (8%)	0 (0%)	
Unknown	8 (10%)	7 (10%)	
Presumed cause of CA			0.03
Cardiac	53 (66%)	55 (81%)	
Other origin	15 (19%)	3 (4%)	
Unknown	12 (15%)	10 (15%)	
Patients sedated with propofol	75 (94%)	66 (99%)	0.22
Propofol dose (mg/kg/h)	2.6 (std 1.1) (range: 0.2 to 6.2)	3.0 (std 1.0) (range: 0.2 to 5.4)	0.01
Patients sedated with midazolam	32 (40%)	19 (28%)	0.14
Midazolam dose (mg/kg/h)*	0.29 (std 0.25) (range: 0.03 to 0.77)	0.25 (std 0.22) (range: 0.03 to 0.67)	0.53
Patients treated with fentanyl	37 (46%)	36 (53%)	0.41
Fentanyl dose (μg/kg/h)	1.7 (std 0.9) (range: 0.6 to 4.7)	1.9 (std 0.6) (range: 0.7 to 2.7)	0.20
Patients treated with remifentanil	24 (30%)	19 (28%)	0.78
Remifentanil dose (μg/kg/h)	4.6 (std 2.9) (range: 1.1 to 13.3)	7.4 (std 4.4) (range: 2.5 to 14.7)	0.02
Patients treated with morphine	19 (24%)	13 (19%)	0.52
Morphine dose (mg/kg/h)*	0.34 (std 0.14) (range: 0.20 to 0.65)	0.28 (std 0.10) (range: 0.16 to 0.58)	0.22

(CPC=cerebral performance category, OHCA=out-of-hospital cardiac arrest, VF=ventricular fibrillation, CA=cardiac arrest.) * Data of the dose levels of propofol, midazolam, and morphine was missing in two patients.

Predicting neurological outcome

At 24 hours after cardiac arrest, 48% of patients with poor neurological outcome showed iso-electric, low voltage, or burst-suppression with identical bursts EEG patterns, against none of the patients with a good neurological outcome. At 12 hours, 56% of the patients with good neurological outcome showed a normal or diffusely slowed EEG pattern, against two patients (4%) with poor neurological outcome. These latter two patients died from non-neurological causes (cardiac shock and a second cardiac arrest) before neurological examination was possible. Sensitivity, specificity, PPV, and NPV

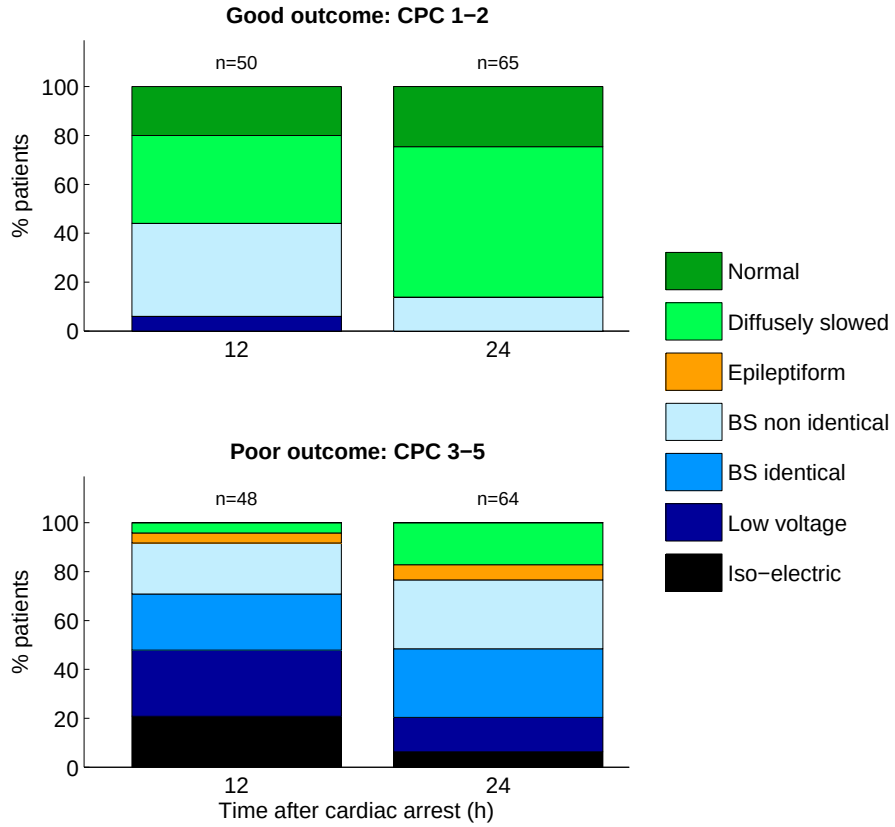

Figure 4.2: EEG patterns at 12 and 24 hours after cardiac arrest for patients with good and poor neurological outcome. In all patients with iso-electric EEG, low-voltage EEG, or burst-suppression patterns with identical bursts after 24 hours, outcome was poor. (CPC=Cerebral performance category, BS non identical=burst-suppression without identical burst, BS identical=burst-suppression with identical bursts.)

of (groups of) EEG patterns for the prediction of good or poor neurological outcome are displayed in Table 4.2.

Epileptiform activity

At 12 hours after cardiac arrest, the EEGs of two patients showed epileptiform activity (evolving seizures). Both still showed this activity at 24 hours. Two additional patients had epileptiform discharges at 24 hours after cardiac arrest. In one of them, this activity consisted of evolving seizures, and in the other of generalized periodic discharges. All four patients had poor neurological outcome, despite treatment with anti-epileptic drugs in three of them.

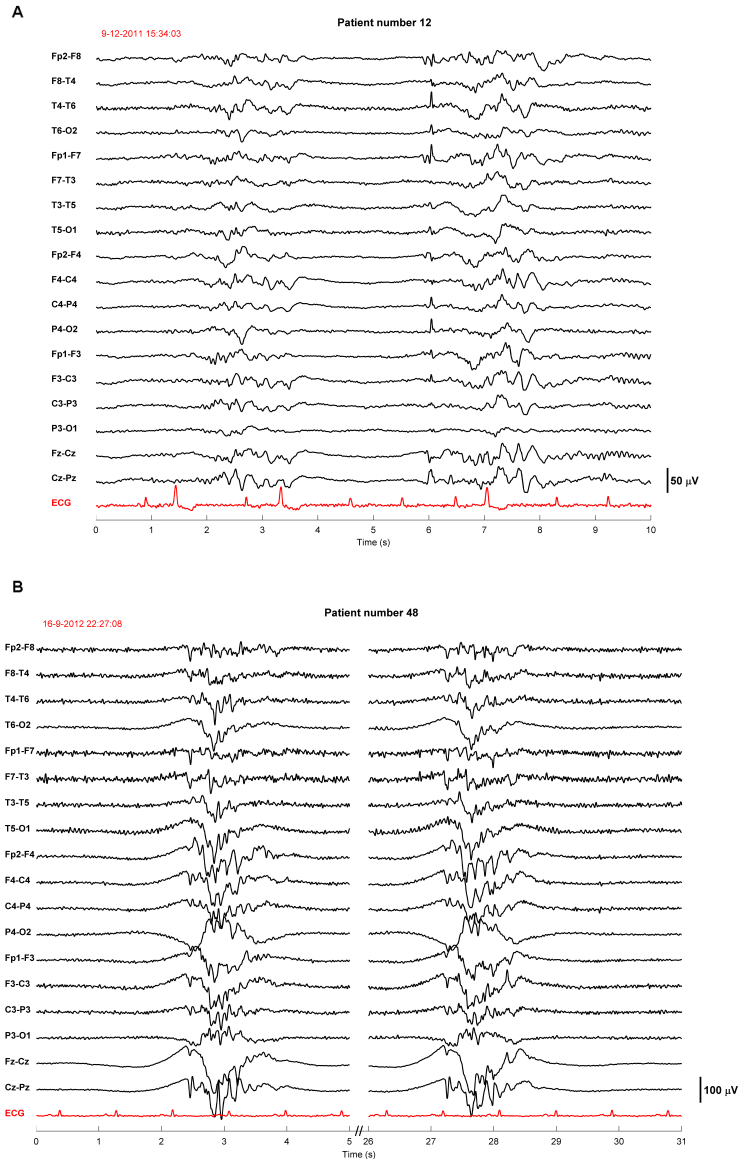

Figure 4.3: Illustrations of burst-suppression patterns without (A) and with (B) identical bursts. These EEGs were recorded in two patients with postanoxic encephalopathy 24 hours after cardiac arrest, treated with mild therapeutic hypothermia (33°C). Filter settings were 0.5-35 Hz. A) This patient received propofol (4.3 mg/kg/h), and had a good neurological outcome (CPC=1). B) This patient received propofol (2.7 mg/kg/h), and had a poor neurological outcome (CPC=5).

Table 4.2: Sensitivity, specificity, and predictive values for early prediction of neurological outcome using EEG.

	Time after resuscitation (h)	Predicting	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)
EEG diffuse slowed or normal	12	Good Outcome	56 (41–70)	96 (86–100)	93 (78–99)	68 (55–78)
EEG iso-electric, low-voltage or burst-suppression with identical bursts	24	Poor Outcome	48 (35–61)	100 (94–100)	100 (89–100)	66 (56–76)

(Sens=sensitivity, Spec=specificity, PPV=positive predicting value, NPV=negative predictive value, CI=confidence interval.)

Discussion

In this prospective cohort study involving the largest reported group of cardiac arrest patients, treated with MTH, we showed that distinct EEG patterns during continuous EEG monitoring at 12 or 24 hours after cardiac arrest reliably predict both good and poor neurological outcome. At 24 hours, iso-electric, low voltage, or burst-suppression with identical bursts patterns predicted poor neurological outcome with a sensitivity of 48% and a specificity of 100%. In contrast, at 12 hours, continuous patterns, either normal or diffusely slowed, predicted good neurological outcome with a sensitivity of 56% and a specificity of 96%.

Our findings are in line with other studies reporting on EEG for prediction of outcome of patients treated with MTH after cardiac arrest. In general, continuous patterns have been associated with good neurological outcome, both during MTH and at normothermia[4,11,13,17,18]. In contrast, iso-electric or low-voltage patterns, burst-suppression, and status epilepticus at normothermia have been associated with poor neurological outcome[4,11,13,17,18]. However, unlike in our study, it was not always clear at which moment after cardiac arrest EEGs were assessed, which limits comparison. Our data show that the time of evaluation from cardiac arrest is critical and that differences of EEG patterns between patients with good versus poor outcome are especially large in the first 24 hours. Therefore, we chose to assess predictive values at 12 and 24 hours. These critical time points were applied based on results of our previous study in 56 patients, which showed that EEG patterns evolve towards less specific patterns

beyond 24 hours after cardiac arrest12. In the current study, besides isoelectric and low voltage patterns, we extended the category of unfavorable EEG with "burst-suppression with identical bursts", a distinct EEG pattern which also appears to be invariably associated with poor neurological outcome[14].

Previously studied parameters for prediction of neurological outcome included prehospital factors (initial cardiac rhythm, age or witnessed versus non witnessed cardiac arrest), as well as clinical (motor score at 72 hours, corneal reflexes and pupillary light responses) and biochemical markers (neuron specific enolase, S-100B)[2–6,19,20]. However, since the introduction of MTH, only bilateral absent SSEP responses at 72 hours and bilateral absent pupillary light reflexes at 72 hours still seem to reliably predict poor outcome, with false positive rates of 0.7% and 0.4% respectively[6], while of no single parameter, predictive values were as high as those of early EEG measures. Why does EEG monitoring perform so well in predicting neurological outcome? The EEG reflects cortical activity, mainly resulting from synaptic activity of pyramidal cells in the cortex[21]. It is generally assumed that synaptic transmission is the first process to fail during cerebral ischemia[22], which makes the EEG signal very sensitive to effects of ischemia[22]. In this study, we did not include clinical parameters, since we focused on the EEG patterns within 24 hours after cardiac arrest in patients treated with MTH. During this time interval, all patients were sedated, limiting conclusive neurological examination. Still, prediction of clinical outcome may be improved and extended to later time points after cardiac arrest by combining neurophysiological, biochemical, and clinical data[6].

In our cohort of 148 patients, four (3%) had epileptiform activity within the first 24 hours. All four had poor neurological outcome. This is in line with previous literature, describing that epileptiform activity is associated with poor outcome, however not inevitably so[17,23–26]. We therefore did not include epileptiform activity or status epilepticus in our criteria for the prediction of poor neurological outcome. More patients from our cohort probably had epileptiform activity at later time points, which was not structurally evaluated. It is unknown whether treatment of these patterns, including generalized periodic discharges, improves outcome[27–31]. To address this issue, a randomized clinical trial to estimate the effect of early and intensive treatment of these patterns should be conducted.

Most of our patients were treated during MTH with propofol, or a combination of propofol and midazolam. Although these sedatives influence EEG patterns, they did not affect the predictive values of the specific EEG patterns in our cohort. Iso-electrical, low voltage, or burst-suppression with identical bursts patterns cannot be solely induced by propofol and/or midazolam. In the relatively low dosages of propofol and midazolam that were used in our patients, the EEG should have remained continuous in patients without postanoxic neuronal damage[32–35]. In burst-suppression patterns induced by propofol, bursts are heterogeneous and appear and disappear gradually[36,37], whereas our identical burst-suppression patterns were all characterized by abrupt transitions between bursts and suppressions[14]. There were no statistically significant differences in type of medication between the patients with good and poor neurological outcome or dosage of midazolam (Table 4.1). The dosage of propofol was slightly higher in patients with a good neurological outcome, which might reflect less severe postanoxic encephalopathy probably resulting in more arousal.

Our study has certain limitations. First, a common problem in unblinded studies investigating the prognostic value of a certain parameter may be the "self-fulfilling prophecy". Although EEGs were scored offline and blinded for the patients' outcome, attending physicians were not blinded for the EEG registration to enable treatment of epileptiform activity. Therefore, the EEG could potentially have influenced clinical decision making regarding to discontinuation of further treatment. However, current guidelines regarding treatment continuation were strictly followed and do not include the EEG during the first 24 hours. A second limitation is the visual analysis of EEGs. Although scoring of the EEGs was performed by two reviewers blinded to the patients' outcome, and according to strict definitions, visual analysis, although gold standard, remains partly subjective. The use of automated, quantitative methods may provide a more objective assessment[15,38,39].

Conclusions

Distinct EEG patterns within 24 hours after cardiac arrest reliably predict both good and poor neurological outcome of patients with postanoxic encephalopathy after cardiac arrest, treated with MTH. At 24 hours after cardiac arrest, the combined group of iso-electric, low voltage, and "burst-suppression with identical bursts" is invariably associated with poor outcome. At 12 hours, normal or diffusely slowed EEG patterns are strongly associated with good outcome. EEG monitoring within the first 24 hours after cardiac arrest may be included in future clinical guidelines.

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Chapter 5

Moderate treatment of electroencephalographic status epilepticus does not improve outcome of comatose patients after cardiac arrest

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Submitted

Abstract

Objective: Electroencephalographic seizures, including status epilepticus, occur in 9–35% of comatose patients after cardiac arrest. Mortality is 90–100%. Most physicians treat these patients with anti-epileptic drugs. However, it is unclear whether (some) seizure patterns represent a condition in which treatment improves outcome, or severe ischemic damage, in which treatment is futile. We studied treatment, including its effects on EEG and outcome, of electroencephalographic seizures and status epilepticus of comatose patients after cardiac arrest.

Design: Retrospective analysis of prospective observational cohort study.

Setting: Medical intensive care units of two teaching hospitals.

Patients: Patients admitted for therapeutic hypothermia after cardiac arrest.

Intervention: None.

Measurements and main results: Thirty-one (22%) out of 139 patients were treated with anti-epileptic drugs (fenytoin, levetiracetam, valproate, clonazepam, propofol, midazolam): two with one, nine with two, thirteen with three, five with four, one with five, and one with six different anti-epileptic drugs. This treatment improved pathological EEG patterns in most patients. However, all but one patients with electroencephalographic status epilepticus died. Outcome was assessed at six months with the Cerebral Performance Category score. In patients with unfavorable EEG patterns at 24 hours after cardiac arrest, including a subgroup with seizures or GPDs, there was no difference in outcome between those treated with and without anti-epileptic drugs. Otherwise, in a subgroup with relatively favorable patterns, the proportion of patients with a poor outcome was lower after treatment with anti-epileptic drugs.

Conclusions: In comatose patients after cardiac arrest, treated with hypothermia, the widely used practice of moderate treatment of electroencephalographic status epilepticus does not improve outcome and can be considered futile. Future studies should focus on early and aggressive treatment.

Introduction

Of comatose patients after cardiac arrest, 40%–66% never regains consciousness as a result of diffuse postanoxic encephalopathy[1–3]. In these patients a broad spectrum of electroencephalography (EEG) changes can be observed[4]. Electroencephalographic seizures or status epilepticus is described in 9%–35%[4–7] and is associated with poor outcome: case fatality was 90%–100% in prospective case series, despite treatment with anti-epileptic drugs[2,6,8–13].

The diagnosis of seizures and status epilepticus on the electroencephalogram (EEG) in comatose patients after cardiac arrest is controversial[14,15]. It may consist of unequivocal seizures: generalized spike-wave discharges at 3/s or faster or clearly evolving discharges of any type at 4/s or faster, either generalized or focal. However, some experts also consider other rhythmic or periodic patterns, such as generalized or lateralized periodic discharges or rhythmic delta activity, as seizure activity[16].

It is unclear whether (some) electroencephalographic seizure patterns in patients with postanoxic encephalopathy represent a condition which can be treated with antiepileptic drugs to improve patients' outcome, or rather severe ischemic damage, in which treatment is futile[17]. Case series have suggested that in patients with electroencephalographic status epilepticus, preserved brainstem reactions and EEG reactivity are associated with a favorable outcome[6]. However, it is unclear whether treatment with anti-epileptic drugs reduces the risk of a poor outcome in these patients and if so, how aggressive this treatment should be. In the only prospective non-randomized intervention study, aggressive treatment up to pentobarbital induced burst-suppression resulted in a good outcome of 6% of patients with clinically overt or electroencephalographic status epilepticus. This proportion is approximately the same as reported in observational studies, irrespective of treatment[6,10–13]. Despite this lack of evidence, most neurologists treat electroencephalographic seizures and status epilepticus in comatose patients after cardiac arrest with anti-epileptic drugs and increased detection with continuous EEG monitoring has led to increased prescription[18,19]. However, only approximately one third treats patients with electroencephalographic status epilepticus equal to those with clinically overt status epilepticus[18,20].

We evaluated treatment, including its effects on the EEG and patient outcome, of seizures and electroencephalographic status epilepticus on continuous EEG

in our prospective cohort study on the prognostic value of continuous EEG monitoring of comatose patients after cardiac arrest on the intensive care unit.

Methods

Patients

We identified patients that were treated with anti-epileptic drugs (fenytoin, levetiracetam, valproate, or clonazepam) for electroencephalographic seizures or status epilepticus from our prospectively collected cohort of comatose patients after cardiac arrest, treated with hypothermia, between June 1st 2010 and March 31st 2013. These patients were included in a prospective cohort study on the predictive value of continuous EEG on outcome in two hospitals in the Netherlands. Design, eligibility criteria, and main outcomes of the first 60 patients that were included in this study have been published previously[4]. In brief, since June 1st 2010, consecutive adult comatose patients after cardiac arrest, treated with hypothermia, were included within twelve hours after the arrest to undergo continuous EEG monitoring on the intensive care unit. Monitoring continued until patients regained consciousness, died, or up to five days. The study was approved by the institutional review board (Medisch Ethische Toetsingscommissie Twente) and informed consent for continuous EEG measurement was waived. Patients' informed consent was asked for clinical follow up.

Treatment

Comatose patients after cardiac arrest were treated according to current standard therapy, as described previously[4]. In short, hypothermia of 33°C was induced as soon as possible after the arrest and maintained for 24 hours by intravenously administered cold saline and cooling pads. Propofol, midazolam, or a combination of these was used for sedation to a level of −4 or −5 at the Richmond Agitation Sedation Scale and discontinued after normothermia had been reached, if possible. Fentanyl, remifentanil, or morphine was used against shivering. Treatment of epileptiform discharges was not included in the study protocol and was left to the discretion of the treating physician. If continuously infused propofol or midazolam dose was increased simultaneously with the initiation of treatment with anti-epileptic drugs, this was considered as anti-epileptic treatment.

EEG recordings

For all recordings, electrodes were applied according to the international 10–20 system, using 19 channels. Electrode impedances were kept below 5 kΩ. Sampling frequency was set to 256 Hz. A Neurocenter EEG system (Clinical Science Systems, the Netherlands) or a Nihon Kohden system (VCM Medical, the Netherlands) was used. Data were stored to disk for off-line analysis.

Outcome assessment

The primary outcome measure of the study was the best score on the Cerebral Performance Category (CPC) within six months dichotomized between "good" (CPC 1 or 2) and "poor" (CPC 3, 4, or 5). Outcome assessment was done at three and at six months after cardiac arrest by telephone by a single investigator (MT-C) that was blinded for treatment with anti-epileptic drugs. Secondary outcome measures included mortality.

EEG analysis

EEG analyses were done at the initiation of and during anti-epileptic treatment, and at 24 hours after cardiac arrest. EEGs first were analyzed independently by two investigators (MT-C, MvP) in automatically selected epochs of five minutes at 24 hours after cardiac arrest. Each epoch was categorized as iso-electric, low voltage, burst-suppression, diffuse slowing, normal, or epileptiform discharges. Epileptiform discharges included unequivocal, evolving seizures and generalized periodic discharges (GPDs). The investigators were blinded for the patients' clinical condition during the registration, the recording time of the epoch, and the patient's outcome. In case of disagreement, the final classification was decided by consensus. These standardized EEG analyses were done after the registrations and EEG played no role in initial treatment decisions with regard to continuation of intensive care treatment. All EEGs of patients who had been treated with anti-epileptic drugs were subsequently reviewed by two observers (JH, MvP), who had access to the complete recordings, but were blinded for the patients' outcome.

Statistical analysis

The number of patients treated with the various anti-epileptic drugs, the proportion of patients in whom this treatment improved the EEG, and the proportion of patients with a poor outcome after treatment are presented in a descriptive way for subgroups according to the EEG patterns at the time of treatment initiation. Patients treated with and without anti-epileptic drugs are compared

Table 5.1: Baseline characteristics of patients treated with and without anti-epileptic drugs.

	Treatment with anti-epileptic drugs	
	Yes (n=31)	No (n=108)
Age (mean years ± SD)	64 ± 11	65 ± 12
OHCA	29	95
Presumed cause of cardiac arrest		
Cardiac	20	82
Other	5	11
Unknown	6	15
Initial rhythm		
VF	21	76
Asystole	6	17
Bradicardia	2	4
Unknown	2	11
Propofol treatment	28	101
Propofol dosage (mg/kg/h, mean ± SD)	3.0 ± 0.7	2.8 ± 1.1
Midazolam treatment	9	36
Midazolam dosage (μg/kg/h, mean ± SD)	211 ± 271	309 ± 252
Fentanyl treatment	17	53
Fentanyl dosage (μg/kg/h, mean ± SD)	1.6 ± 0.7	1.8 ± 0.8
Remifentanil treatment	9	33
Remifentanil dosage (μg/kg/h, mean ± SD)	4.7 ± 2.3	4.2 ± 0.7
Morphine treatment	3	23
Morphine dosage (μg/kg/h, mean ± SD)	331 ± 148	309 ± 119

SD indicates standard deviation; OHCA, out of hospital cardiac arrest; VF, ventricular fibrillation; dosage, maximum dosage within the first 24 hours.

with regard to poor outcome for subgroups according to the EEG patterns at 24 hours after cardiac arrest, which are known to be related to outcome[4]. Data are presented as proportions and odds ratio's, including corresponding 95% confidence intervals.

Results

March 31st 2013, 139 patients had been included (108 in Medisch Spectrum Twente and 31 in Rijnstate Hospital). Baseline characteristics are presented in 5.1. Blinded EEG evaluation could be performed in 121 at 24 hours. Analysis at 24 hours of other EEGs was not possible in case of artifacts in the automatically selected five minute epochs.

Thirty-one patients (22%) were treated with anti-epileptic drugs. This treatment was initiated at a median of 47 hours after cardiac arrest (interquartile range 36-76). Two patients were treated with one, nine with two, thirteen with

three, five with four, one with five, and one with six different anti-epileptic drugs. Three of these patients had evolving seizures, twelve GPDs, and nine burst-suppression, during more than 30 minutes. Examples are shown in Figures 5.1 and 5.2. Burst-suppression patterns that had been treated with anti-epileptic drugs consisted of bursts resembling epileptiform discharges with duration of one up to tens of seconds and flat inter-burst intervals. All but one patients with evolving seizures, GPDs, or burst suppression treated with anti-epileptic drugs had a poor outcome and died (Tables 5.2 and 5.3). The only patient with a good outcome had GPDs intermixed with physiological activity. Five patients with short episodes of rhythmic delta activity of three up to ten seconds, and three with isolated sharp waves, both superimposed on diffusely slowed, but continuous patterns, were treated with anti-epileptic drugs. These all had a good outcome.

In Table 5.4, patients treated with and without anti-epileptic drugs are compared with regard to the risk of poor outcome for subgroups according to the EEG patterns at 24 hours after cardiac arrest. There were no statistically significant differences in the subgroups with relatively unfavorable EEG patterns (iso-electric or low voltage, and burst suppression, evolving seizures, or GPDs). Otherwise, in patients with diffusely slowed or normal EEG patterns at twelve or 24 hours after cardiac arrest, the proportion of patients with a poor outcome was lower after treatment with anti-epileptic drugs.

Discussion

In this prospective observational study in comatose patients after cardiac arrest, treated with hypothermia, retrospective analysis of moderate treatment with anti-epileptic drugs yielded no evidence for effect on outcome of patients with electroencephalographic status epilepticus: all but one patients with evolving seizures, GPDs or burst suppression treated with anti-epileptic drugs had a poor outcome and died. However, all patients that had been treated with anti-epileptic drugs because of short episodes of rhythmic delta activity or isolated sharp waves superimposed on diffusely slowed, but continuous patterns had a good outcome. Among patients with these relatively favorable EEG patterns[4,21] the proportion of patients with a poor outcome was lower after treatment with anti-epileptic drugs.

Many of our patients that were treated with anti-epileptic drugs fulfilled the criteria for status epilepticus by semiology, EEG appearance, and duration. Still,

Table 5.2: Anti-epileptic drugs with their effects on EEG patterns and clinical outcome.

Drug (n)	EEG pattern (n)	Improved EEG n (%)	Poor outcome n (%)
Fenytoin (25)	Evolving seizures (1)	1 (100%)	1 (100%)
	GPD (11)	6 (55%)	11 (100%)
	Burst suppression (8)	3 (38%)	8 (100%)
	Isolated sharp waves (1)	1 (100%)	0
	Intermittend rhythmic delta (4)	4 (100%)	0
Levetiracetam (7)	Evolving seizures (2)	1 (50%)	2 (100%)
	GPD (2)	1 (50%)	2 (100%)
	Burst suppression (1)	1 (100%)	1 (100%)
	Isolated sharp waves (1)	0	0
	Intermittend rhythmic delta (1)	1 (100%)	0
Valproate (11)	Evolving seizures (3)	2 (67%)	3 (100%)
	GPD (3)	1 (33%)	2 (67%)*
	Burst suppression (1)	0	1 (100%)
	Isolated sharp waves (2)	1 (50%)	0
	Intermittend rhythmic delta (2)	2 (100%)	0
Clonazepam (9)	Evolving seizures (1)	n.a.	1 (100%)
	GPD (3)	2 (67%)	3 (100%)
	Burst suppression (1)	1 (100%)	1 (100%)
	Isolated sharp waves (1)	0	0
	Intermittend rhythmic delta (3)	3 (100%)	0
Propofol (8)	Evolving seizures (0)	-	-
	GPD (5)	3 (60%)	4 (80%)*
	Burst suppression (1)	0	1 (100%)
	Isolated sharp waves (1)	n.a.	0
	Intermittend rhythmic delta (1)	1 (100%)	0
Midazolam (5)	Evolving seizures (0)	-	-
	GPD (2)	0	2 (100%)
	Burst suppression (2)	0	2 (100%)
	Isolated sharp waves (0)	-	-
	Intermittent rhythmic delta (1)	1 (100%)	0

Fenytoin initial dosage 1000–1500 mg followed by 200–300 mg daily in two doses. Levetiracetam 1000–1500 mg daily in two doses. Valproate initial dosage 1000–1800 mg followed by 1000–1500 mg daily in two doses. Clonazepam single or repeated bolus of 1 mg. Propofol 200–400 mg/hr. Midazolam 8–10 mg/hr. Burst-suppression patterns consisted of bursts resembling epileptiform discharges of one up to five seconds and flat interburst intervals. Improved EEG pattern indicates temporary suppression of evolving seizures, reduction of amplitude of generalized periodic discharges (GPD) or burst-suppression, disappearance of isolated sharp waves, or reduction of amplitude and rhythm of intermittent rhythmic delta activity; EEG, electroencephalography; n.a. not assessable; *, in the only patient with GPDs and a good outcome, GPDs were intermixed with physiological activity.

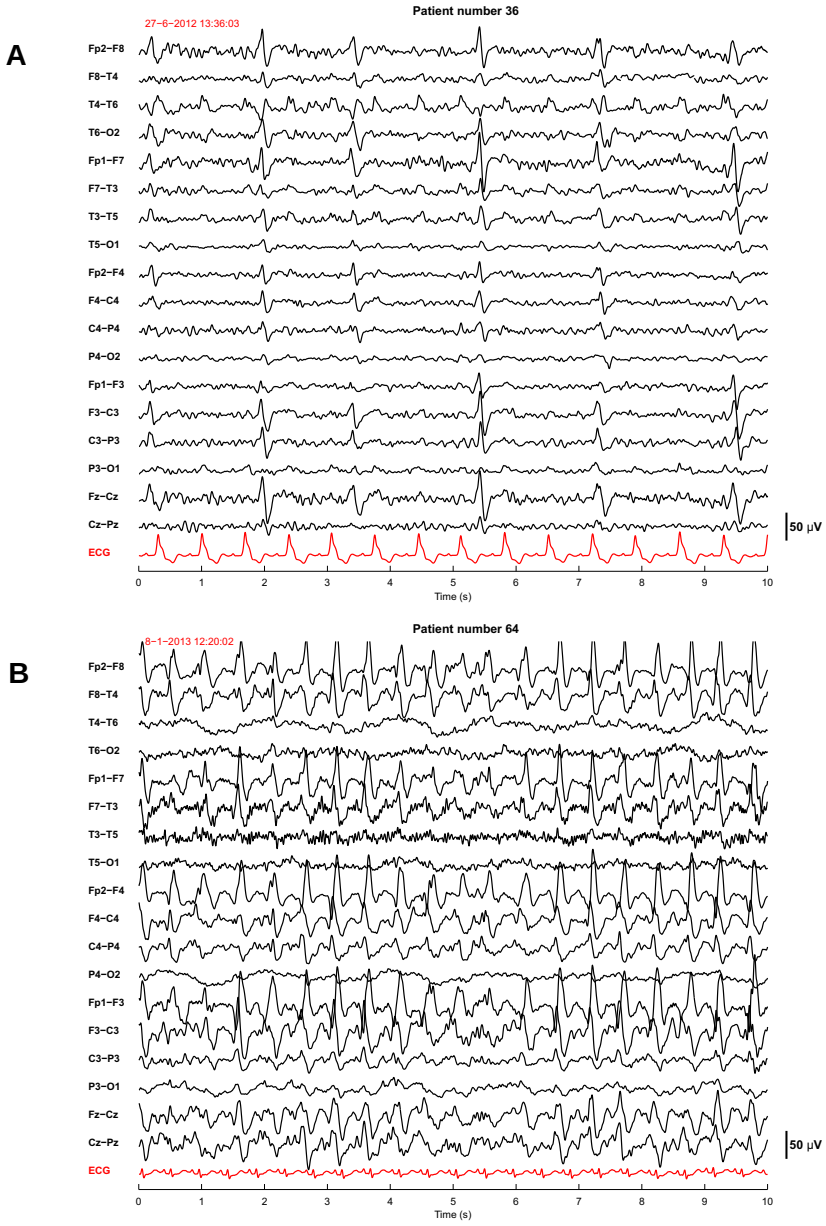

Figure 5.1: Examples of EEGs of two comatose patients after cardiac arrest showing generalized periodic discharges. These patients were normothermic and sedated with propofol 1 to 2.5 mg/kg/hr. The EEG epochs were recorded 46 hours (A) or 68 hours (B) after cardiac arrest. Filter settings 0.5–30 Hz.

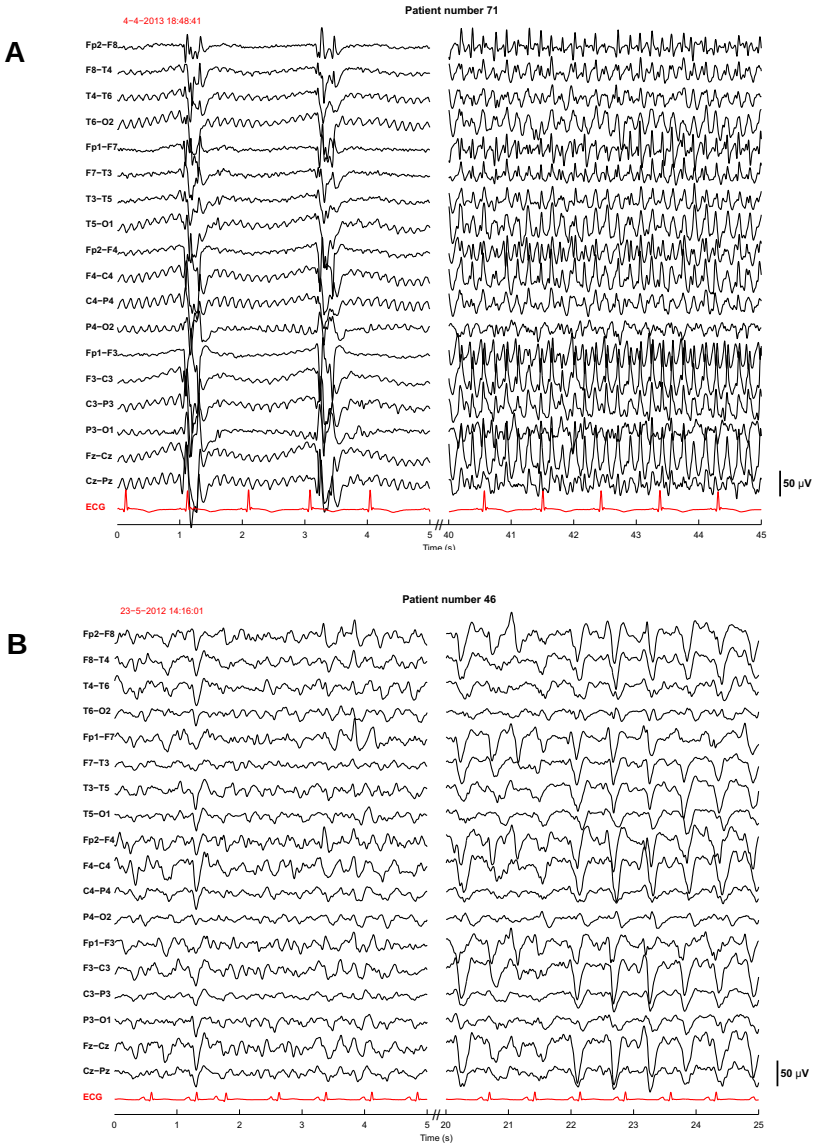

Figure 5.2: Examples of EEGs of two comatose patients after cardiac arrest showing evolving seizures. These patients were sedated with propofol 1 to 2.5 mg/kg/hr. The EEG epochs were recorded 19 hours after cardiac arrest, during therapeutic hypothermia (33°C) (A), or 78 hours after cardiac arrest, after restoration of normothermia (B). Filter settings 0.5–30 Hz.

Table 5.3: Proportions of patients with improved EEG or poor outcome after treatment with (combinations of) anti-epileptic drugs, according to the EEG pattern at the initiation of treatment.

EEG pattern at initiation of treatment (n)	Improved EEG n (%)	Poor outcome n (%)
Evolving seizures (3)	3 (100%)	3 (100%)
GPD (12)	9 (75%)	11 (92%)
Burst suppression (9)	3 (33%)	9 (100%)
Isolated sharp waves (2)	2 (100%)	0
Intermittent rhythmic delta (5)	5 (100%)	0

Two patients were treated with one, nine with two, thirteen with three, five with four, one with five, and one with six different anti-epileptic drugs. Burst-suppression patterns consisted of bursts resembling epileptiform discharges of one up to five seconds and flat inter-burst intervals. Improved EEG indicates temporary suppression of evolving seizures, reduction of amplitude of generalized periodic discharges (GPD) or burst-suppression, disappearance of isolated sharp waves, or reduction of amplitude and rhythm of intermittent rhythmic delta activity; EEG, electroencephalography; n.a. not accessible; *, in the only patient with GPDs and a good outcome, GPDs were intermixed with physiological activity.

Table 5.4: Proportions of patients with poor outcome treated with or without anti-epileptic drugs according to EEG pattern at 24 hours after cardiac arrest.

EEG pattern at 24 hours	Poor outcome with AED n/N (%)	Poor outcome without AED n/N (%)	OR (95% CI)
Iso-electric or low voltage (n=12)	5/5 (100%)	7/7 (100%)	n.a.
Evolving seizures, GPD, or burst suppression (n=46)	14/17 (82%)	23/29 (79%)	1.1 (0.4 to 3.1)
Continuously slowed (n=61)	0/5 (0%)	7/54 (13%)	0.9 (0.8 to 1.0)

AED indicates anti-epileptic drugs; OR, odds ratio of poor outcome of patients treated with as compared to patients treated without AED; 95% CI, 95% confidence interval.

all were treated only moderately and in none of them treatment induced burst-suppression EEG. If these patients indeed had an electroencephalographic status epilepticus, they were probably not treated sufficiently, especially since treatment of status epilepticus in general improves outcome if directed at suppression of electroencephalographic epileptiform discharges[22]. The moderation of treatment in our cohort is representative for the general ambivalence towards treatment of electro-encephalographic seizures in comatose patients after cardiac arrest[18,20]. This moderation reflects the uncertainty with regard to the use of this treatment in these patients.

Apart from the intensity of treatment, the onset of treatment probably plays an important role. With continuous EEG monitoring starting twelve hours after

cardiac arrest, we found that in approximately one quarter of patients with electroencephalographic status epilepticus, the epileptiform patterns started before 24 hours after cardiac arrest. In previous studies, EEG monitoring only started at a median of two to three days after cardiac arrest, indicating that diagnosis and subsequent treatment of electroencephalographic status epilepticus started thereafter at its earliest[6,10,12]. Mechanisms such as excessive glutamate release are known to worsen brain damage in ongoing status epilepticus within twenty to forty minutes[23]. Also, prolonged duration of status epilepticus reduces the effect of treatment, e.g. due to receptor trafficking[24]. Thus, the initiation of treatment many hours after the onset of electroencephalographic status epilepticus may be too late to prevent irreversible damage.

Previous studies have focused on electroencephalographic status epilepticus as a predictor of poor outcome after cardiac arrest and the identification of patients in whom treatment of status epilepticus might be beneficial. These have shown that sporadic patients with postanoxic encephalopathy after cardiac arrest and electroencephalographic status epilepticus may survive[4,12,13,21]. Identified possible determinants of a favorable outcome include a continuous background pattern[21], preserved brainstem reactions, and EEG reactivity[6]. However, even in survivors, it remained unclear whether or not (aggressive) treatment had improved outcome, since electroencephalographic status epilepticus after cardiac arrest is often spontaneously transient[6].

We found a possible beneficial effect of anti-epileptic drugs on outcome of patients with relatively favorable EEG patterns, suggesting a neuroprotective effect. The only neuroprotective treatment of proven benefit so far in comatose patients after cardiac arrest is therapeutic hypothermia[1]. A randomized controlled trial on the effect of prophylactic treatment with anti-epileptic drugs is ongoing (http://clinicaltrials.gov/ct2/show/NCT01083784).

This study has limitations. First, although data on patient outcome and EEG patterns were pre-specified and collected prospectively, data on the use of anti-epileptic drugs were retrieved retrospectively, implying possible observation or selection bias. Second, since evidence of effect for treatment is lacking, there was no treatment protocol. Therefore, both the nature and the intensity of treatment differed among physicians. However, treatment never reached an intensity to induce burst-suppression EEG and barbiturates were not used. Third, although the Glasgow Coma Scale score was measured daily, infor-

mation on other clinical parameters had not been collected prospectively, and retrospective collection appeared unreliable. Therefore, the proportion of patients with clinically overt myoclonic status epilepticus was unclear. However, in patients after cardiac arrest, for both electroencephalographic seizures and clinical myoclonia it is not clear whether these represent "true" seizures, with a possibility to return to physiological activity, or an expression of severe (irreversible) damage[25]. For most neurologists the threshold to treat patients with overt myoclonia is lower than for patients with non-convulsive electroencephalographic seizures. However, irreversible damage is probably even more likely in patients with myoclonia, since the risk of poor outcome is larger[6] and neuronal necrosis is more common[25]. Fourth, we selected patients based on treatment with specific anti-epileptic drugs and only identified continuously infused propofol or midazolam as a treatment against electroencephalographic seizures, if dosages increased simultaneously with the initiation of treatment with anti-epileptic drugs. We cannot exclude that in some patients electroencephalographic seizures were treated solely with propofol or midazolam.

Conclusion

In comatose patients after cardiac arrest, treated with hypothermia, general practice of treatment of electroencephalographic status epilepticus includes moderate treatment with anti-epileptic drugs. Although widely used, such treatment does not improve patients' outcome and can be considered futile. Future studies should focus on early and aggressive treatment.

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Part II

Signal Analysis

Chapter 6

A novel approach for computer assisted EEG monitoring in the adult ICU

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Abstract

Objective: The implementation of a computer assisted system for real-time classification of the electroencephalogram (EEG) in critically ill patients.
Methods: Eight quantitative features were extracted from the raw EEG and combined into a single classifier. The system was trained with 41 EEG recordings and subsequently evaluated using an additional 20 recordings. Through visual analysis, each recording was assigned to one of the following categories: normal, iso-electric, low voltage, burst suppression, slowing, and EEGs with generalized periodic discharges or seizure activity.
Results: 36 (88%) recordings from the training set and 17 (85%) recordings from the test set were classified correctly. A user interface was developed to present both trend-curves and a diagnostic output in text form. Implementation in a dedicated EEG monitor allowed real-time analysis in the intensive care unit (ICU) during pilot measurements in four patients.
Conclusions: We present the first results from a computer assisted EEG interpretation system, based on a combination of eight quantitative features. Our system provided an initial, reasonably accurate interpretation by non-experts of the most common EEG patterns observed in neurological patients in the adult ICU.
Significance: Computer assisted EEG monitoring may improve early detection of seizure activity and ischemia in critically ill patients.

Introduction

Evaluation of the brain function in patients from the intensive care unit (ICU) is important, since these patients are at risk of several secondary brain injuries such as (non-convulsive) seizures, cerebral ischemia and increased cerebral pressure[1,2]. Clinical examination of these critically ill patients is however limited, even more so when they are sedated and ventilated[2–4]. Monitoring of the brain in these patients is therefore highly desirable. Neuroimaging provides good anatomical information, but its functional information is very often limited and typically of a discontinuous nature[2,5]. Since the electroencephalogram (EEG) is sensitive to changes in brain activity caused by both epileptic seizures and ischemia, continuous EEG (cEEG) can provide a useful tool for real-time brain monitoring[1,2,4,6–9]. Among others, Jordan et al. evaluated the usefulness and clinical impact of cEEG monitoring in the neuroscience ICU. They concluded that 86% of all cEEG recordings in the neuroscience ICU had an impact on clinical management[10].

Despite the potential clinical relevance of cEEG monitoring in the ICU, its use in many ICUs remains limited. One of the main reasons for this involves the complex and time-consuming task of interpretation of each recording by means of visual analysis[1,5,8]. Raw EEG can hardly be interpreted by non-experts, which includes most ICU nurses and ICU physicians. To overcome this problem, several attempts have been made in computer-assisted real-time detection of deteriorations in brain function by extracting quantitative EEG (qEEG) features from the raw data. Such systems make earlier diagnostics and treatment possible. For example, various qEEG features have been proposed to detect seizures[11–14], to identify vasospasms after subarachnoid hemorrhage[15,16], to differentiate between patients with good neurologic outcomes and those with poor outcomes after cardiac arrest[17,18], and to predict the clinical outcome of (sub-) acute stroke patients[19–21]. However, these features have only focused on specific patient categories.

Ideally, all feature types should be combined into one overall system capable of classifying the common EEG patterns observed in the ICU with reasonable accuracy. This will allow unambiguous interpretation of the EEG by ICU personnel. The patterns to detect in the adult ICU should include normal EEGs, iso-electric EEGs, low voltage EEGs, burst suppression patterns, EEGs with regional or diffuse slowing (e.g. due to ischemia in post-anoxic and stroke patients, contusions in trauma patients or postictal slowing), EEGs with seizure

activity, and EEGs with generalized periodic discharges (GPDs). In addition, an adequate representation of the information is required, providing relevant information to ICU personnel in a simple and clear manner, while presenting a more detailed analysis (including raw EEG data) to the consulting neurologist or clinical neurophysiologist.

This paper describes the implementation of a real-time EEG classification system based on a combination of several qEEG features. The creation of such a system is a first step towards real-time, computer-assisted detection of deteriorations in brain function, including seizure activity and ischemia in critically ill patients.

Methods

Patient data

EEG data for training and evaluation was selected from the digital EEG database of the Medisch Spectrum Twente hospital. All EEG registrations in the database were classified by experienced electroencephalographers using standard visual analysis. Both training and test set contained a representative set of EEG patterns. At least one 5 min epoch was selected in each EEG, reviewed by an experienced electroencephalographer (MvP) for a second time, and assigned to one of the above described categories. Uniform epochs were used so that each of them contained only a single EEG pattern. In addition, only epochs with minimal or no artefacts were used (as judged from visual inspection) with the exception of three. These three epochs contained many artefacts and were used for an initial training step to detect artefacts. The epoch selection and second review by the electroencephalographer was done prior to the automated epoch classification by our system. Therefore, the classification by the electroencephalographer was blinded to the output of the system.

All EEGs were recorded with 19 electrodes placed on the scalp according to the 10–20 system. The impedances were kept below 5 kOhm to reduce polarization effects and the sampling frequency was either 250 Hz or 256 Hz. All recordings were made using a BrainLab EEG recording system (OSG BVBA, Belgium) or Neurocenter EEG (Clinical Science Systems, Leiden, Netherlands). The Institutional Review Board waived the need for medical ethical assessment and informed consent, since all recordings were performed as a standard procedure in the clinical evaluation of the patients.

Training set
The training set consisted of 41 EEG epochs with a duration of 5 min each, recorded from 39 different patients. Thirty-five of these patients were admitted in the ICU, three were healthy outpatients with normal EEGs and one patient was admitted to the stroke unit. To train the system for artefact detection, three epochs were included that contained a considerable amount of artefacts.

Test set
An independent test set, containing epochs from different patients than included in the training set, was used for the evaluation. Seventeen of these recordings were from ICU patients and three were from outpatients. All selected epochs contained artefact free, 5 min duration EEG data. To prevent a selection bias, the test set was selected from the EEG database by a physician who was naive for the current study. Details of the training and test set are summarized in Tables 6.1 and 6.2.

Evaluation in the ICU
Real-time pilot measurements were performed in four ICU patients to evaluate the technical feasibility of the classifier during real-time EEG registrations.

Feature extraction

The implementation of the system was divided into several steps. First, all signals were filtered by a zero-phase 6th order butterworth bandpass filter (from 0.5 to 30 Hz) and transformed to both source and longitudinal bipolar montages. Subsequently, eight qEEG features were calculated. Based on these features, a classification was made for every 10 s segment by using a decision tree. Finally, a single interpretation for each 5 min epoch was determined. All routines were implemented in Matlab (The Mathworks Inc.). A set of features was calculated for each 10 s segment of EEG. Most features, except for the Brain Symmetry Index (BSI) and burst and suppression index were calculated after re-referencing the EEG to the source montage. To limit the potential contribution of eye blink artefacts, the two most frontal channels Fp1 and Fp2 were discarded for these feature types. To calculate the burst and suppression index, all 19 channels (including Fp1 and Fp2) were used. The longitudinal bipolar derivations F4–C4, C4–P4, P4–O2, F3–C3, C3–P3, P3–O1, F8–T4, T4–T6, T6–O2, F7–T3, T3–T5, and T5–O1 were used to calculate the BSI. For both the burst and suppression index and the BSI, a single value was obtained for the complete 10 s EEG epoch. This is in contrast with the rest of the features, which provided a value for each individual channel separately.

Table 6.1: Results of the training set. In column 3, "c" and "x" denotes correctly and incorrectly classified epochs respectively. BS=burst suppression pattern, DS=diffuse slowing, RS=regional slowing, GPDs=Generalized periodic discharges, PAE=post-anoxic encephalopathy.

Patient no.	EEG pattern	Results	Remarks
1–4	Normal	c	One ICU patient and three outpatients.
5–7	Iso-electric	c	Two EEGs had ECG artefacts.
8	Low voltage	c	
9	BS (with several types of artefacts)	x	Suppressions were missed because of the artefacts. A correct warning about artefacts was given.
10a	BS (bursts contains EMG activity)	c	Interpreted as high frequency artefacts.
10b	Same EEG as 10a, but after an injection with a muscle relaxant (Esmeron).	c	Interpreted as a burst suppression pattern.
11–13	BS	c	
14	BS	x	Interpreted as slowing, because most (low amplitude) bursts were missed.
15–16	DS in a patient with PAE.	c	
17a	DS + RS in a neurotrauma patient.	c	
17b	Same EEG as no. 17a, but a few hours later after further deterioration.	c	
18–22	DS + RS in a neurotrauma patient.	c	
23	DS in a neurotrauma patient.	x	One brain region was interpreted as seizure activity instead of slowing
24	RS in a neurotrauma patient.	c	
25–26	DS + RS in a post-surgical patient.	c	
27	DS + RS in a stroke patient.	c	Measured in the stroke unit.
28	DS + RS in a coma patient.	c	
29	DS + GPDs in a patient with PAE.	x	(Low amplitude) GPDs were missed, the DS was classified correct.
30	GPDs in a neurosurgery patient.	c	
31–34	GPDs	c	
35–36	Nonconvulsive status epilepticus.	c	
37–38	DS + EMG artefacts.	c	
39	DS + high amplitude artefacts.	x	Artefacts were interpreted as seizure activity.

Table 6.2: Results of the test set. In column 3, "c" and "x" denotes correctly and incorrectly classified epochs respectively. BS=burst suppression pattern, DS=diffuse slowing, RS=regional slowing, GPDs=generalized periodic discharges, PAE=post-anoxic encephalopathy.

Patient no.	EEG pattern	Results	Remarks
1–2	Normal EEG	c	Measured in outpatients.
3–4	Iso-electric	c	
5	Low voltage EEG, but normal EEG.	x	ECG artefacts were interpreted as bursts.
6	Low voltage EEG, but normal EEG.	x	Measured in an outpatient. Most epochs were interpreted as normal and not as low voltage.
7–10	BS	c	Two with long (>20 sec) and two with short (<10 sec) interburst intervals.
11–12	DS in a patient with PAE.	c	
13–14	DS + RS in a neurotrauma patient.	c	
15	DS + RS in a coma patient.	c	
16	DS + RS in a surgical patient.	c	
17	DS + GPDs	x	GPDs were missed, the DS was classified correct.
18	GPDs	c	
19	Seizure activity and/or GPDs.	c	
20	Nonconvulsive status epilepticus.	c	

For the features based on the power spectrum, a power spectral density was estimated using Welch's averaged periodogram method. Each 10 s segment of EEG was windowed for each channel and detrended using a Hamming window with a length of 512 sample points. The resulting spectra from each segment were averaged and one spectral density with a resolution of approximately 0.5 Hz was obtained per channel.

Mean amplitude

The mean amplitude of the EEG was primarily used to classify iso-electric EEGs and low voltage EEGs. In addition, signals with very high mean amplitudes were interpreted as containing either seizure activity or artefacts, depending on the outcome of the other features. The mean amplitude of each channel was calculated as the mean of the absolute value of that channel.

Frequency analyses

The alpha to delta ratio (ADR)[16,20,22] and spectral edge frequency (SEFx)[23] were used to detect slowing of the EEG patterns. The ADR is calculated as the power ratio between the alpha (8–13 Hz) and delta band (0.5–4 Hz). The SEF_x is the frequency below which a certain percentage (denoted by x) of the total power is located. In this study, the SEF_{90} was used and the total power was defined as the power between 0.5 and 15 Hz. To detect high frequency artefacts such as those caused by muscle contractions, we introduced a "high to low frequency power ratio": the power ratio between 25–30 Hz and 0.5–25 Hz.

Burst and suppression index

For the detection of burst suppression patterns and GPDs, a novel burst and suppression index was introduced as illustrated in Figure 6.1. First, the signal was pre-processed with a non-linear energy operator (NLEO), defined as

$$\phi(n) = |(x_{n-1} \cdot x_{n-2}) - (x_n \cdot x_{n-3})|, \tag{6.1}$$

where x_n denotes the current sample of signal x, x_{n-1} the first sample before sample n, etc.[14]. This pre-processed signal shows which parts of the EEG have a high local energy (high amplitude and/or high frequency). A moving threshold was used to detect the energy increases in the signal. The running threshold was set at four times the mean plus four times the standard deviation of the preceding 0.5 s of the signal, with a minimum of 10 μV^2. After the detection of a burst, the 0.5 s that followed were ignored to prevent a single burst from being detected more than once. This was performed for all 19 channels. A burst was required to be present in more than 10 channels simultaneously (within a window of 0.2 s) to be classified as a true burst. Suppressions were detected in a comparable way. The same NLEO was applied to the EEG, but the threshold for the detection of suppressions was fixed at 5 μV^2. If the amplitude of the signal was below this value for more than 1.5 s in 10 or more channels at the same time, it was interpreted as a suppression. A 10 s epoch of EEG was interpreted as a burst suppression pattern if at least one burst and one suppression were detected in that epoch. GPDs were detected with the same method as the burst detection method. Generally, GPDs occur multiple times in a 10 s epoch. Therefore, 10 s of EEG with three or more bursts and without any suppressions were interpreted as GPDs.

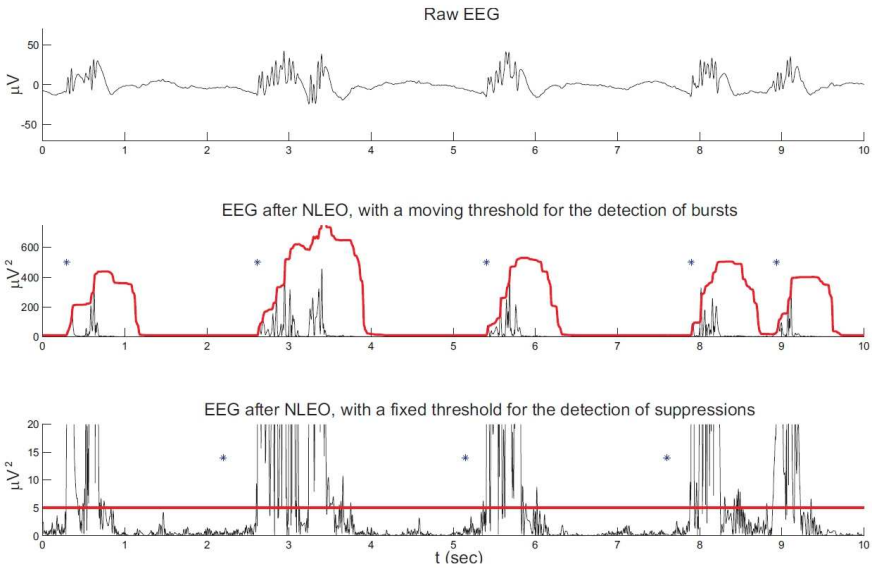

Figure 6.1: Burst and suppression index for one channel. The raw EEG is shown in the upper plot and the middle plot shows the same EEG after applying a NLEO (black) together with a running threshold (red) for the detection of bursts. The threshold is based on the mean and standard deviation of the previous 0.5 s of the signal. The detected bursts are marked with blue asterisks. The bottom plot shows the same EEG after the NLEO was applied, but the *y*-axis is scaled. The red line in this figure represents the fixed threshold for the detection of suppressions. A suppression is detected (marked with a blue asterisk) if the signal is below this threshold for more than 1.5 s.

Nearest neighbor coherence

The nearest neighbor synchronization is the coherence between a particular electrode and its surrounding (nearest neighbor) electrodes[8]. Since synchronization is often increased during seizure activity, this feature was chosen as one of the features for the detection of seizures. The nearest neighbor coherence was implemented as the mean coherence between each channel and its neighbors in the frequency range between 0.5 and 15 Hz.

Periodicity based on autocorrelation analysis

The periodicity of the EEG is often increased during seizures as well. To detect epochs with an increased periodicity, a measure for periodicity was used based on autocorrelation. This was done similar to the method proposed by Deburchgraeve et al. and Liu et al.[14,24]. First, the autocorrelation functions for each window of 5 s were calculated with an overlap of 4 s. This was done for all channels. The zero-crossings in these autocorrelation functions

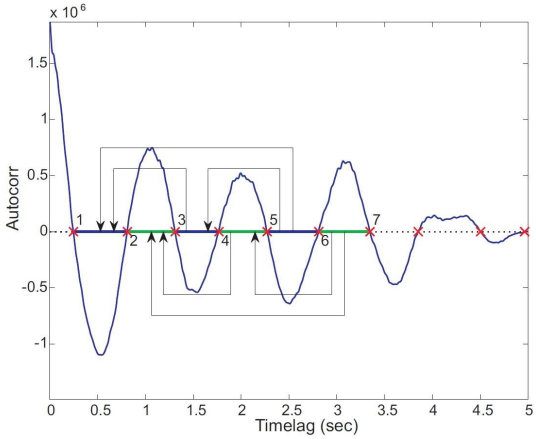

Figure 6.2: Autocorrelation of an EEG epoch with seizure activity. Intervals between the zero-crossings of this autocorrelation are regular. The arrows indicate which intervals are compared (each interval is used twice

were then detected. To be classified as true zero-crossings, the maximum autocorrelation value and the time interval between two zero-crossings had to be larger than a given threshold. After detecting the zero-crossings, the ratios between different zero-crossing intervals were calculated. An example of this is shown in Figure 6.2. The mean value of these ratios was used as a measure for the periodicity. The value approaches 1 for signals with high periodicity and becomes higher or lower than 1 for signals without periodicity. If less than four or more than sixty zero-crossings were present, the signal was considered as non-periodic, and the measure of periodicity was not calculated. Also, epochs with very low energy (mean value of a signal of less than 2 μV^2 after applying NLEO) were ignored. The measure for periodicity was calculated for each channel and for each 5 s window. The measures for each window in a single epoch were averaged per channel and the ignored epochs were discarded. This resulted in a single value per channel per epoch. In some cases, all windows of a channel were ignored in the calculation. These channels were then interpreted as non-periodic.

Brain Symmetry Index

The Brain Symmetry Index (BSI) was designed to detect asymmetries between the left- and right hemispheres of the brain[25–27]. In this study, we used a pairwise derived variant of the BSI comparable to the variant recently introduced

by Sheorajpanday et al.[21]. For this variant, the BSI is defined as

$$\mathrm{BSI}(t) = \frac{1}{MK} \sum_{ch=1}^{M} \sum_{n=1}^{K} \left| \frac{R_{n,ch}(t) - L_{n,ch}(t)}{R_{n,ch}(t) + L_{n,ch}(t)} \right|, \tag{6.2}$$

with for channels in the right hemisphere, and a similar expression for channels in the left hemisphere. Here, K is the number of Fourier coefficients and M is the number of channel pairs, while denotes the Fourier coefficient with index n of channel ch evaluated at time t. Hereby, t corresponds to a particular epoch $[t - T, t]$ with duration T. A period of 10 s was used for T and the BSI was calculated in the frequency range from 0.5 to 25 Hz with a spectral bandwidth of 0.5 Hz. The BSI is bounded in range between zero (perfect symmetry for all channels) and 1 (maximum asymmetry). The pairwise variant of the BSI was used to increase the sensitivity for abnormalities that affect different regions in both hemispheres (for example patients with traumatic brain injury). In contrast to the study of Sheorajpanday et al., we used a bipolar longitudinal montage in the calculation of the pair-wise derived variant of the BSI.

Classification: decision tree

To preserve relevant information about localization and time, our system classified each 10 s epoch in four defined brain regions: left anterior, left posterior, right anterior and right posterior. The left anterior region consisted of channels F8, F4, Fz, T4, C4 and Cz, the left posterior region T3, C3, Cz, T5, P3, Pz and O1, the right anterior region F7, F3, Fz, T3, C3 and Cz, and the right posterior region T4, C4, Cz, T6, P4, Pz and O2. To obtain a classification per region, the feature values of all channels in that region were averaged and used in the decision tree. Since the periodicity measure did not necessarily have a value for each channel, the third lowest value of all non-discarded channels in each brain region was used.

A decision tree was constructed based on the prior knowledge about EEG patterns in several conditions as encountered in ICU patients. In this way, we tried to mimic the way a neurologist would describe the EEG. After the initial design, the decision tree was improved by using EEG recordings from the training set. In several steps, the boundary values and the order of the features were adapted to improve the outcome of the classified training set. For each step, we analyzed which EEG patterns were classified incorrectly and for what reason. Focus was not only placed on the percentage of falsely classified patterns, but we also considered the severity of a misclassification in clinical practice. For example, the detection of patterns with seizure activity

Table 6.3: The most common EEG patterns and the quantitative EEG features used to classify these patterns. The features are listed in the same order as they appear in the decision tree.

EEG Pattern	Quantitative EEG feature
Iso-electric	Mean amplitude
Low voltage	Mean amplitude
Artefacts	High to low frequency ratio, mean amplitude
Burst suppression	Burst and suppression index
GPDs	Burst and suppression index
Seizure activity	Autocorrelation, nearest neighbour synchronization, mean amplitude
Slowing	Spectral edge frequency and alpha to delta ratio
Normal	-

and slowing was implemented with a cut-off value which had a relatively high sensitivity (and lower specificity), while it was decided to be more conservative with the definition of an iso-electric EEG by limiting the sensitivity for that category. Table 6.3 shows which features were eventually used to classify each pattern. The final version of the decision tree was applied on the training set again, and afterwards on the independent test set.

In general, the most discriminating features should appear first in the decision tree[28]. For our system, the mean amplitude was the most discriminating feature; EEGs with very low mean amplitudes can only be iso-electric or low-voltage and almost all other features cannot be defined reliably. Similarly, EEGs with high mean amplitudes typically contain burst suppression patterns, seizure activity or (high amplitude) artefacts. The mean amplitude was therefore the first feature evaluated in the tree. Subsequently, EEG epochs with an increased “high to low frequency power ratio” were classified as epochs with artefacts, since further classification of signals with many artefacts is unreliable. Then, the presence of bursts and suppressions was evaluated to detect burst suppression patterns and GPDs. If the signal did not contain any bursts, the EEG was tested for seizure activity by evaluating the synchronization, periodicity and amplitude. The seizure activity check was performed after the detection of GPDs, since GPD patterns can also have an increased amplitude, synchronization and periodicity. Two less specific features were the SEF and ADR. Although they are very sensitive for the detection of slowing, these features are only useful when other EEG abnormalities (such as seizure activity) are excluded. For this reason, the SEF and ADR values were placed at the bottom of the tree, to distinguish slowed EEG patterns from normal EEG registrations. Diagrams of the full decision tree are presented in Figures 6.3 and 6.4.

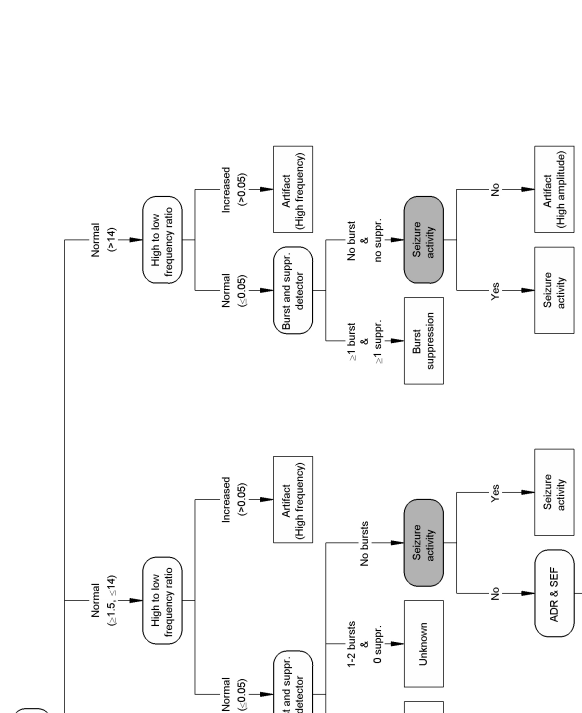

Figure 6.3: Structure of the decision tree for the classification of the EEG per 10 s epoch and per brain region (left anterior, left posterior, right anterior, right posterior). In this figure, the gray colored "Seizure Activity Tree" blocks represent a smaller decision tree (shown in Figure 6.4). ECG artefacts can increase the mean amplitude of an iso-electric EEG significantly. Therefore, the boundary for the mean amplitude between "extremely low" and "decreased" is increased to 1 μV in EEG signals with a high correlation to the ECG signal. All other boundaries in the decision tree are fixed. ADR=Alpha to delta ratio, SEF=Spectral edge frequency.

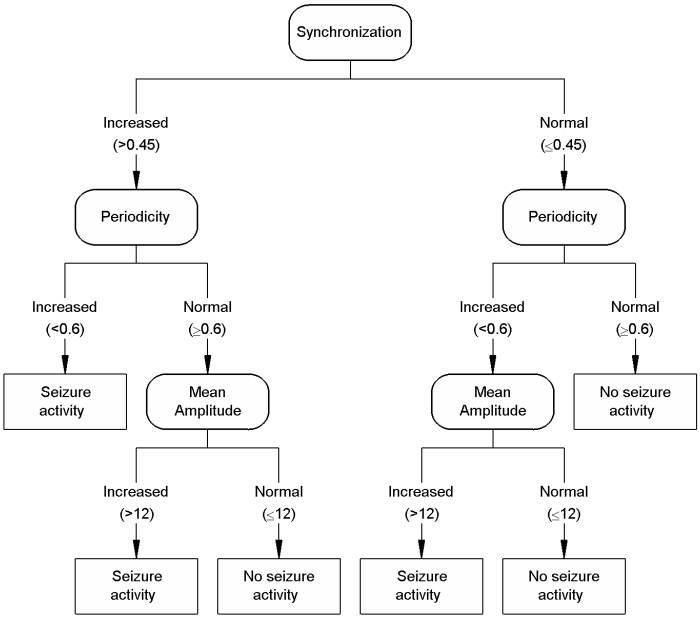

Figure 6.4: Decision tree for the detection of seizure activity. This tree represents the gray colored "Seizure Activity Tree" blocks in the overall decision tree of Figure 6.3. This smaller decision tree is used to detect whether an epoch contains seizure activity, and its output is either "No" (no seizure activity) or "Yes" (seizure activity). This decision is made based on a combination of synchronicity, periodicity and mean amplitude of the EEG signal. After this decision, the remainder of the overall decision tree is used for the final categorization of the epoch.

User interface

The output of the decision tree is displayed in a novel user interface. The user interface of two epochs of the test set are shown together with a small part of the raw EEG in Figure 6.5. The upper left part of the interface consists of four plots, one for each brain region, with the output of the decision tree as a function of the epoch number. In the two upper figures on the right side, the trend of the BSI and the power spectrum of both hemispheres are shown. Since asymmetries can only be measured when the activity of left and right hemispheres are compared, the BSI cannot be calculated for each brain region separately and is therefore displayed separately. In the bottom part of the interface, the interpretation of the preceding 5 min recording is presented in a textbox for each brain region separately. This interpretation is equal to the most prevalent output of the decision tree for each brain region in this time frame. Two exceptions are made for iso-electric EEGs and burst suppression

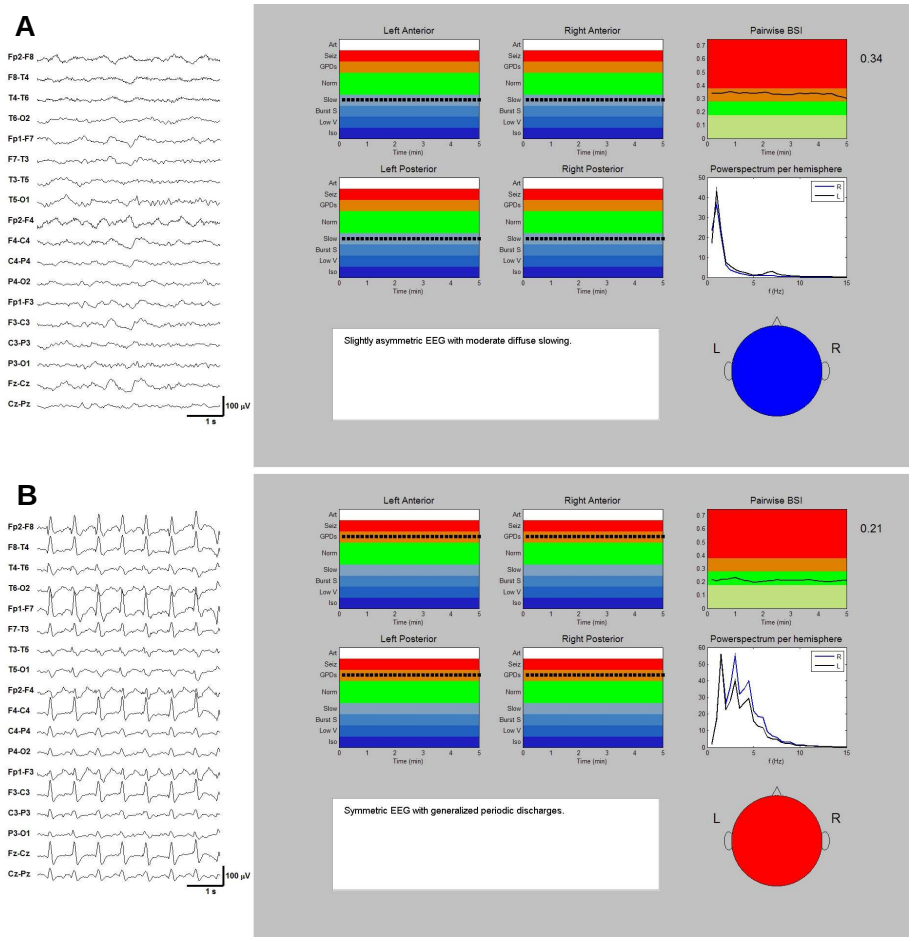

Figure 6.5: Two examples of the user interface showing the results for two registrations of the test set, together with a small part of the raw EEG. The results of the decision tree are displayed in the interface as trend curves (upper panels) and in text (lower left panel). (ART=artefact, Seiz=seizure activity, GPDs=generalized periodic discharges, Norm=normal, Slow=slowing, Burst S=burst suppression, Low V=low voltage, Iso=iso-electric and BSI=Brain Symmetry Index). A: User interface of a neurotrauma patient with diffuse slowing (patient no. 14). B: User interface of an EEG epoch containing GPDs (patient no. 18).

patterns with long suppressions. To classify an EEG as iso-electric, all four brain regions have to be iso-electric for the complete 5 min. If not, the EEG is interpreted as low voltage. If most of the epochs were interpreted as iso-electric or low voltage, and a few as burst suppression, the EEG was interpreted as a burst suppression pattern with long interburst intervals.

In addition to these outputs, a range of possibilities was introduced for the interpretation of the BSI: EEGs were classified as “symmetric”, “slightly asymmetric” or “asymmetric”. In a diffuse slowed EEG, the degree of diffuse slowing (“severe slowing”, “slowing” or “moderately slowing”) was displayed as well. Finally, the computer interpretation of the last 5 min was illustrated using a color coded head. This head displays a brain region as red for seizure activity or GPDs, gray for normal EEGs, blue for slowing, burst suppression or low voltage EEGs, or black for iso-electric EEGs.

Implementation for real-time analysis

Our interpretation algorithms were implemented into the Neurocenter EEG monitoring system of the Medisch Spectrum Twente (Neurocenter EEG, Clinical Science Systems, Netherlands). Instead of using Matlab, the scripts were executed in the GNU Octave open source platform (www.octave.org).

Results

The results obtained from evaluating the training set with the final version of the decision tree are given in Table 6.1. In the training set, 36 out of 41 EEGs (88%) were classified correctly. Two out of the five misclassifications can be explained by artefacts. One of them was an EEG with a burst suppression pattern. The suppressions were not detected due to artefacts in the signal, although a correct warning about the presence of artefacts was given. In the other EEG, artefacts were wrongly interpreted as seizure activity instead of high amplitude artefacts. Two other misclassifications were caused by either missing bursts or GPDs with low amplitudes. The final EEG was misclassified in a single brain region, where slowing of the EEG was classified as seizure activity, the other three brain regions were classified correctly as slowing.

After optimizing the decision tree with the training set, an evaluation was done on a new independent test set. The outcome of this evaluation is shown in Table 6.2. Seventeen out of twenty EEGs (85%) were classified correctly. Of the three incorrect interpreted EEGs, two were low voltage EEGs. One of the low voltage EEGs contained many ECG artefacts and these were interpreted as bursts. This caused the EEG to be misclassified as a burst suppression pattern. The second low voltage EEG was classified as normal. The last misclassified EEG was caused by missing GPDs with low amplitude.

The real-time implementation of our system was evaluated in four ICU patients. Simulations in a Matlab environment showed that the algorithm was

fast enough for real-time implementation; however the Octave implementation of Neurocenter was much slower. In fact, the current Octave version of the classifier allowed analysis of only the first 10 s of each 30 s in real-time, while the other 20 s had to be discarded. The raw EEG data was stored without interruption to be available for review by the consulting neurologist. No other technical problems occurred during the measurements. For each of the four registrations, the classifier showed satisfying correspondence between our system and human interpretation. An example of the interface in a long term (4 h) registration is shown in Figure 6.6. At the beginning of the registration, the EEG was mainly diffuse slowed with superimposed muscle contraction artefacts. At the end of the EEG, the pattern showed GPDs and periods of burst suppression which was interpreted correctly by the classification algorithm. In this particular case, this was initially noted by the interpretation of the user interface. Subsequent reviewing of the raw EEG data indeed showed GPDs. The patient was treated for a non-convulsive status epilepticus and recovered well.

Discussion

Monitoring brain function in the ICU is very important, since ICU patients are at high risk of various secondary brain injuries such as seizures or cerebral ischemia. Although the EEG is very sensitive in detecting changes in the neurological status of patients, cEEG monitoring in the ICU is limited due to the fact that the signals are difficult to interpret by non-experts. A reliable real-time classification system will reduce the drawback of the visual interpretation burden and will facilitate the use of cEEG in the ICU. This should allow earlier diagnosis of ischemic events and seizure activity. With the current availability of treatments for acute ischemia, the early detection of cerebral ischemia (in a reversible state) has great potential for infarct prevention[6]. Seizures after brain injury are associated with a less favorable clinical outcome[9,29], and early detection and treatment can most likely improve the outcome. Early detection of seizures with cEEG is therefore very relevant to protect the brain from seizure-related injury in critically ill patients[29,30].

In this study, we present an EEG classification system for monitoring ICU patients, based on a combination of eight qEEG features. Thirty-six EEG epochs out of 41 (88%) and 17 epochs out of 20 (85%) were classified correctly in the training and test set respectively. These results indicate that the system can have a significant impact in the clinical setting. For example, the group

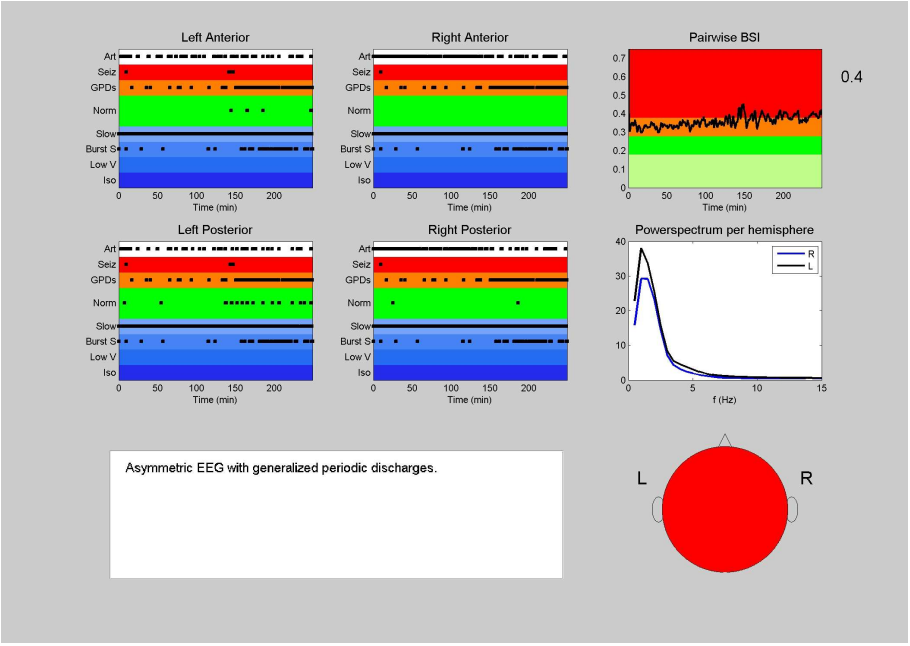

Figure 6.6: The user interface of a long EEG registration (>4 h) for patient no. 1. Initially, the EEG shows a diffuse slowed pattern with many EMG artefacts. After a few hours it evolves into GPDs and an occasional burst suppression pattern. The conclusion (represented as the color coded map and in text) is based on the preceding 5 min of EEG. (ART=artefact, Seiz=seizure activity, GPDs=generalized periodic discharges, Norm=normal, Slow=slowing, Burst S=burst suppression, Low V=low voltage, Iso=iso-electric and BSI=Brain Symmetry Index).

of slowed EEGs was classified very well, showing that early detection and treatment of ischemic events is possible. Although our algorithms do not yet reach the classification accuracy of an experienced electroencephalographer, it does allow for an initial evaluation by non-EEG experts and facilitates the use of cEEG monitoring in the ICU. A regular review of the EEG data by electroencephalograhpers remains of course an essential part in the decision making process.

The two low voltage, but otherwise normal EEGs included in the test set were both misclassified, most likely because of insufficient training the decision tree on low voltage EEGs: only one low voltage EEG was included in the training set. Because of this, the chosen boundary for the mean amplitude between normal and low-voltage might have been chosen too low. In one of the misclassified low voltage EEGs, many ECG artefacts were interpreted as bursts and this was misclassified as a burst suppression pattern. The second

low voltage (but normal) EEG was classified as normal; therefore the misclassification would have had minimal clinical impact. Although great care was taken to select artefact-free epochs, various registrations included in the test set did contain artefacts. Most of the misclassifications were caused by the presence of these artefacts or by missing low amplitude bursts or GPDs. We tried to train the system in handling EEGs with artefacts by including three registrations with artefacts in the training set. However, we are well aware that the number of different artefacts is much larger than three and that the present system is not sufficiently trained for all artefact types. As the reliable detection of artefacts is highly relevant in the daily use of a system in the ICU, additional improvements for the detection of artefacts are required.

It is well known that critically ill patients with GPDs have a poor prognosis for survival, but at present it is not clear if treating or preventing GPDs will lead to an improved outcome in these patients[9,31–33]. There is no consensus regarding the need to treat GPDs or how aggressively they should be treated[34]. Therefore, the clinical consequences of missing GPDs by the classifier are unclear.

A novel interface for our classification system was presented. The text output and color coded head in the interface allow a quick interpretation by non-EEG experts. Extra panels in the interface present additional information to the neurologist and clinical neurophysiologist, and the raw EEG data can still be reviewed by the consulting neurologist or clinical neurophysiologist. The dynamics of longer EEG registrations can be seen with a single glance at the four time-curves representing the output of the decision tree for each of the four brain regions.

In the comparison with the clinical evaluation, we used the output of the classifier. Therefore, there was no additional visual interpretation of the trend curves in the user interface. Of course, it is possible that the EEG shows significant changes within 5 min which may limit the performance of the classifier. Therefore, for our present evaluation we decided to use uniform EEG epochs.

The system was implemented in a dedicated EEG monitor suitable for real-time analysis in the ICU. Pilot measurements performed in four neurological ICU patients showed that the real-time use of the classification system at the bedside of the patient is technically feasible. However, we note that the current

real-time implementation of the classifier allowed analysis of the first 10 s of each 30 s epoch only, while the other 20 s had to be discarded for computational reasons. With more efficient routines, faster software, and higher processing speeds, skipping epochs should not be necessary. Given the typical time scales during which changes occur however, this does not seem to be a critical issue. The evaluation of our system in four real-time registrations was satisfying. Our first impression was that the performance in these registrations was similar to those obtained in the offline analysis. An extended evaluation in a larger group of ICU patients is currently in progress.

Similar to the observations presented in the study of Claassen et al.[30], recordings in our patients showed that continuous monitoring is highly relevant to reliably detect seizure activity. The use of cEEG registrations and computer interpretation had an impact on the clinical decision making in all four of the patients who were monitored in the ICU.

The classification accuracy of the test set and the results of the real-time pilot measurements are encouraging, but it is clear that an evaluation on a larger group of EEGs is needed for additional testing and improvements. The addition of an alarm mechanism to the real-time monitor may also further improve the clinical impact of the system. Integration with other clinical measures such as blood pressure, temperature, intracranial pressure[10], near-infrared spectroscopy[35], drug intake and video[6,36] can further contribute to improved brain monitoring in the ICU, ultimately resulting in the realization of a multidimensional monitoring system[37].

The main focus of our study was to explore whether computer assisted EEG diagnostics can assist in the visual interpretation by experienced electroencephalographers. We did not evaluate the reproducibility of the EEG classification, although this is an important issue. Since the system has been trained by labeled EEG data from the same department, it cannot excluded that there is a particular bias in the classification. Therefore, training and evaluating the system using a larger dataset of different centres may improve the performance of the classifier.

In closing, we remark that most existing real-time EEG systems focus on the detection of seizures or one specific EEG pattern. Particularly in neonates, several automatic seizure detection systems have been proposed[11,14,24,38,39].

However, the EEG in neonates is not comparable to the EEG in adult patients. What makes our system unique is that the classification of most common EEG patterns encountered in the adult ICU is combined into one system. In addition, the classifier is patient independent and no patient specific boundaries or parameters have to be set.

In conclusion, we present a decision tree using eight qEEG features to classify the most common EEG patterns in the adult neurological ICU. This allows us to differentiate between the most common EEG patterns: normal, iso-electric, low voltage, burst suppression, focal or diffuse slowing, GPDs and seizure activity. At present, we achieve a satisfying classification accuracy of 85%. The monitoring system allows real-time classification and subsequent interpretation by ICU personnel. Ultimately, this can contribute to an increased use of real-time EEG monitoring in ICU patients, thereby allowing early detection of neurological derangements and introducing the potential for early interventions.

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Chapter 7

A Cerebral Recovery Index (CRI) for early prognosis in patients after cardiac arrest

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Abstract

Introduction: EEG monitoring in patients treated with therapeutic hypothermia after cardiac arrest may assist in early outcome prediction. Quantitative EEG (qEEG) analysis can reduce the time needed to review long-term EEG, and makes the analysis more objective. In this study we evaluated the predictive value of qEEG analysis for neurological outcome in postanoxic patients.

Methods: In total 109 patients admitted to the ICU for therapeutic hypothermia after cardiac arrest were included, divided over a training and a test set. Continuous EEG was recorded during the first 5 days or until ICU discharge. Neurological outcomes were based on the best achieved Cerebral Performance Category (CPC) score within 6 months. Twenty-seven out of 56 patients (48%) of the training set and 26 out of 53 patients (49%) of the test set achieved good outcome (CPC 1–2). In all patients a 5 minute epoch was selected each hour, and five qEEG features were extracted. We introduced the Cerebral Recovery Index (CRI), which combines these features into a single number.

Results: At 24 hours after cardiac arrest, a CRI<0.29 was always associated with poor neurological outcome, with a sensitivity of 0.55 (95% Confidence interval (CI): 0.32–0.76) at a specificity of 1.00 (CI: 0.86–1.00) in the test set. This results in a positive predictive value (PPV) of 1.00 (CI: 0.73–1.00) and a negative predictive value (NPV) of 0.71 (CI: 0.53–0.85). At the same time point a CRI>0.69 predicted good outcome, with a sensitivity of 0.25 (CI: 0.10–0.14) at a specificity of 1.00 (CI: 0.85–1.00) in the test set, and a corresponding NPV of 1.00 (CI: 0.54–1.00) and a PPV of 0.55 (CI: 0.38–0.70).

Conclusions: We introduced a combination of qEEG measures expressed in a single number, the CRI, which can assist in prediction of both poor and good outcome in postanoxic patients, within 24 hours after cardiac arrest.

Introduction

Early prognosis in patients with postanoxic encephalopathy after cardiac arrest is limited, especially due to treatment with mild hypothermia and sedation[1,2]. In only 34–60% of patients treated with hypothermia after cardiac arrest, consciousness will return[3–5]. Electroencephalography (EEG) monitoring may assist in early prognosis[6–9]. However, analysis of long-term EEG registrations is very time-consuming and can only be done by an experienced electroencephalographer[10–14]. Furthermore, visual EEG interpretation will always be partially subjective[11,14].

Quantitative EEG (qEEG) analysis can reduce the time needed to review long-term EEG, and makes the analysis more objective[12–14]. Additionally, qEEG analysis can be used to reveal and display trends in EEG patterns over longer time periods[13]. Thereby it can be used as a manner to study time constants of improvement in the EEG. In a cohort of 30 patients Wennervirta et al. showed that individual qEEG features such as the burst-suppression ratio, the response entropy, and the state entropy differed between good and poor outcome groups during the first 24 hours after cardiac arrest[15]. A response entropy of ≤12.53 and a subband entropy of ≤11.84 at 24 hours after cardiac arrest both had a sensitivity of 78% and a specificity of 81% for predicting poor neurological outcome[15]. These results are promising, and could possibly be improved by using a combination of multiple qEEG features integrated as a single index.

In this study we analysed five qEEG features and combined these into the Cerebral Recovery Index (CRI), which provides a single number that can be used for prognostication in patients treated with mild hypothermia after cardiac arrest.

Materials and Methods

Patients

From June 2010 to February 2013 we monitored all patients after cardiopulmonary resuscitation, who were admitted to the ICU of our hospital (Medisch Spectrum Twente, Enschede, The Netherlands) for therapeutic hypothermia. A detailed description of patient inclusion criteria was already given in[8]. In short, all adult patients (aged > 18 years), who were resuscitated after a cardiac arrest, remained comatose, and were admitted to the intensive care unit (ICU) to receive therapeutic hypothermia (at 33°C, maintained for 24 hours) were

included. Patients with additional neurological injuries were excluded. The data of the first patients (from June 2010 to July 2011), which we also used in our previous study on the evaluation of predictive value of visual analysis of the EEG[8], were used as training data to define qEEG features and optimize parameter settings. The EEG recordings of the patients included after July 2011 were used as test data, and therefore only used for evaluation. The Institutional Review Board of the Medisch Spectrum Twente waived the need for informed consent for EEG monitoring during ICU stay and for the follow-up after 3 and 6 months by telephone. However, for additional electrophysiological and clinical evaluation after discharge from the ICU in the first 60 patients, local institutional review board approval and written informed consents were obtained.

EEG recordings

EEG recordings were started as soon as possible after the patients' arrival on the ICU and continued up to 5 days or until discharge from the ICU. For practical reasons, EEG recordings were not started late at night. Instead, for patients admitted to the ICU after 11 PM, the recordings were started the next morning at 7 AM. Twenty-one silver-silver chloride cup electrodes were placed on the scalp according to the international 10–20 system. Recordings were made using a Neurocenter EEG recording system (Clinical Science Systems, Voorschoten, The Netherlands). All EEG analyses were performed offline. EEG data played no role in actual prognostication of outcome or treatment decisions. However, the treating physicians were not completely blinded to the EEG to allow treatment of epileptiform discharges. Treatment of epileptiform activity was left at the discretion of the treating physician. Generalized periodic discharges were also interpreted as epileptiform activity, and treated with anti-epileptic drugs. However, no treatment protocol existed for treatment, since evidence for effect of treatment is lacking. Therefore, both the nature and the intensity of treatment differed among physicians. In general, only moderate levels of anti-epileptic drugs were given, and treatment never reached an intensity to induce burst-suppression EEG and barbiturates were not used.

Selecting EEG epochs

EEG epochs of 5 minutes were automatically selected every hour during the first 48 hours after resuscitation and every 2 hours during the remainder of the registration. In this selection, the EEG epoch with the least number of artefacts was chosen, after applying an artefact detection algorithm. In this algorithm,

EEG data from 10 minutes before until 10 minutes after the selected time point was assessed. The EEG data of these 20 minutes was divided into 30 seconds segments. For each segment a value for the amount of artefacts was determined by calculating the number of high voltage peaks (movement artefacts), the power ratio between frequencies inside the EEG range and higher frequencies (muscle activity), and the number of channels that contains zeros (unstacked wires or loose electrodes). Finally, the ten consecutive segments with the lowest summed artefact values were selected, resulting in a 5 minute epoch. In EEG registrations with too many artefacts during the complete 20 minutes, no epoch was selected for that selection moment.

Quantitative EEG features
First, all epochs were filtered by a zero-phase 6th order Butterworth bandpass filter (0.5 to 30 Hz) and transformed to the source derivation. Subsequently, the qEEG analysis was performed. Five features were used: the power, the Shannon entropy, the alpha to delta ratio, the regularity (a feature we developed to distinguish burst-suppression patterns from continuous EEG patterns), and coherence in the delta band. These features were motivated by the criteria which a neurologist evaluates during visual analysis of an EEG. After calculating the values of the five qEEG features, all features were normalized between 0 and 1 with a smooth exponential function, and combined into one overall score, the Cerebral Recovery Index (CRI).

All qEEG features, except the feature for regularity of the amplitude, were first calculated per EEG channel and per 10 seconds segment separately and subsequently averaged over time and over all channels. The regularity feature was calculated per channel for the complete 5 minutes at once, and then averaged over all EEG channels.

Power: To quantify the power of the EEG, the standard deviation (SD) of the EEG was calculated. As the mean of the signal can be expected to be negligibly small after filtering, the SD is equivalent to the mean power of the signal.

Shannon Entropy: An analytical technique to quantify the irregularity of a stochastic signal is entropy. Overall, entropy describes the complexity, or unpredictability of a signal. In this study we used the Shannon entropy (H_{Sh}),

first defined by Shannon and Weaver as:

$$H_{sh} = -\sum_{i=1}^{N} p(x_i) log_2 p(x_i), \tag{7.1}$$

where x_i is the amplitude of the signal and $p(x_i)$ the probability of its occurrence in the signal segment[16,17]). The probability density function $p(x_i)$ was estimated by using the histogram method where the amplitude range of the signal was linearly divided into bins (from –200 μV to 200 μV, with a bin width of 1 μV.)

Alpha to delta ratio: The alpha to delta ratio (*ADR*)[13,18–20] was calculated as the power ratio between the alpha (8–13 Hz) and delta frequency band (0.5–4 Hz). To calculate this power ratio, a power spectral density was estimated using Welch's averaged periodogram method using a Hamming window with a length of 2 s resulting in a spectral density estimation with a resolution of 0.5 Hz.

Regularity: To separate burst-suppression patterns from continuous EEG patterns (with a regular, constant amplitude) we developed a feature to evaluate the regularity of the amplitude of a signal. In Figure 7.1 we present two signals as an example. Figure 7.1A shows a signal with a high variance in amplitude and Figure 7.1B a signal with more regular amplitude. In this technique we first squared the signal and applied a moving average filter with a window of 0.5 s to create a non-negative smooth signal. The window length of the moving average was set at 0.5 s. A longer window would average out the differences in activity between subsequent bursts and suppressions, while a shorter window length would not average out the individual peaks within one burst. Subsequently, we sorted the values of the smoothed signal in "descending" order (see Figure 7.2). The normalized standard deviation of this sorted signal was then calculated as a feature for regularity (*REG*) in amplitude of the data:

$$REG = \sqrt{\frac{\sum_{i=1}^{N} i^2 q(i)}{\frac{1}{3} N^2 \sum_{i=1}^{N} q(i)}}, \tag{7.2}$$

with N the length of the signal in samples and q the sorted signal. The nominator calculates the standard deviation of the sorted signal, which is normalized in a range between 0 and 1 by the denominator. The REG value of a signal with constant amplitude is 1, independent of the amplitude of the signal. A

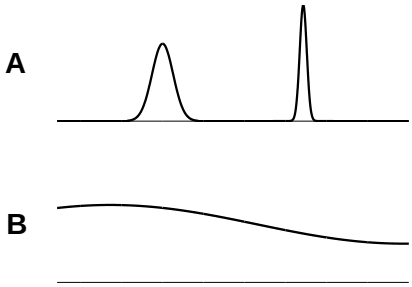

Figure 7.1: Example of two signals with different variance in amplitude. The signal in A shows two short periods with high amplitude on a zero background, the variance in amplitude in this signal is relatively high, while the signal in B has a more regular or constant amplitude. The signal in A can be compared with an EEG showing a burst suppression pattern, while the signal in B can be compared with an EEG with continuous amplitude. This is expressed in the regularity index (cf. Equation 7.2 and Figure 7.2).

signal with relatively low amplitude (suppression) that contains a short period of higher amplitude (burst) will have a value close to zero; if there are more or longer bursts the REG value will increase. Two examples of this technique applied on EEG data showing a burst-suppression pattern and a normal EEG pattern are given in Figure 7.2 A and B respectively. Note that the REG value for the burst-suppression EEG (Figure 7.2A) is lower than of the normal continuous EEG (Figure 7.2B), indicating that the burst suppression EEG shows more spread in amplitude.

Coherence in the delta band: To quantify EEG patterns with an abnormal high synchronization level, the mean coherence (*COH*) in the delta band (0.5–4 Hz) between all possible combinations of EEG channels was implemented. In the calculation of the coherence we used a Hann window with a length of 4 s and an overlap of 2 s.

Feature Combination

Finally, the five qEEG features were combined into a single number, the Cerebral Recovery Index (CRI). First the value of each qEEG feature was normalized in the range from 0 to 1, with 0 corresponding to a pathological EEG and 1 corresponding to a physiological EEG. These normalized qEEG scores (annotated with a hat) are schematically displayed in Figure 7.3 and expressed as:

$$\widehat{SD} = 1/(1 + e^{-2(SD-2.5)}), \tag{7.3}$$

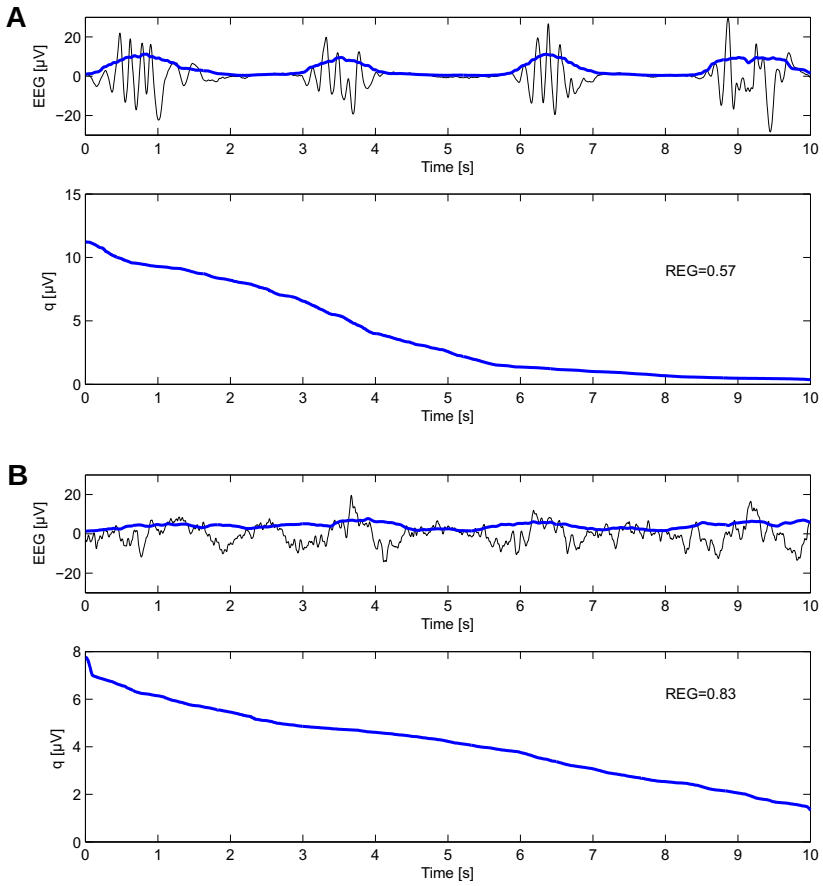

Figure 7.2: Calculating the regularity of the amplitude (REG) in an EEG showing a burst suppression pattern (A) and a diffusely slowed pattern (B). In the top graphs, the raw EEG is shown (black), together with the EEG after squaring and applying a moving average filter (with a window of 0.5 s) (blue). In the bottom graphs, the signal q is obtained after sorting this smoothed signal in decreasing order. The calculated value for the regularity (REG) is the normalized variance of this sorted signal q (cf. Equation 7.2). REG is normalized from 0–1, where a higher value corresponds to a signal with a more regular amplitude as illustrated.

$$\widehat{H_{Sh}} = 1/(1 + e^{-9(H_{Sh}-2.5)}), \tag{7.4}$$

$$\widehat{ADR} = 1/(1 + e^{-10(ADR-0.5)}), \tag{7.5}$$

$$\widehat{REG} = 1/(1 + e^{-10(REG-0.65)}), \tag{7.6}$$

and

$$\widehat{COH} = 1/(1 + e^{10(COH-0.45)}). \tag{7.7}$$

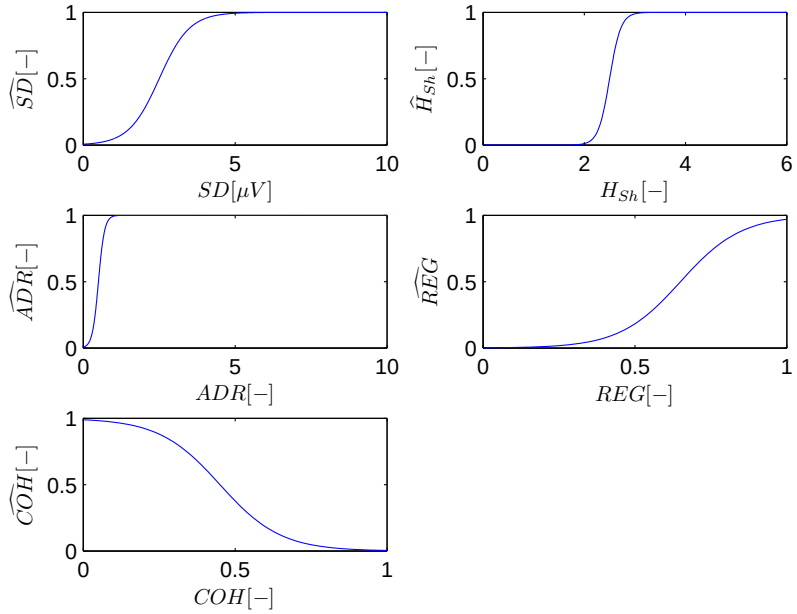

Figure 7.3: Normalized qEEG scores. All five qEEG values are normalized using a smooth sigmoid function (Equations 7.3–7.7), resulting in score for each feature (annotated with a hat) between 0 and 1. (SD=standard deviation, H_{Sh}=Shannon entropy, ADR=alpha to delta ratio, REG=regularity, COH=coherence.)

The values for the parameters in these expressions were set after visual inspection of the data of the training set. We did this for each feature independently, selecting the data that was most relevant for that specific feature. For example, for the REG feature we compared burst-suppression EEGs with normal EEGs showing continuous activity, while for the SD feature we compared iso-electric and low-amplitude EEGs with continuous EEGs.

As the power of an EEG signal is a requirement for a normal EEG - if there is no power at all, the EEG is flat and all other features are useless - in the combined score, ($\widehat{SD}$) was multiplied with the mean of the other four qEEG scores. However due to the sigmoid shape of the curve for $\widehat{SD}$ (Equation 7.3, Figure 7.3), the value of the CRI is independent for further changes in power once the power has reached a certain minimal threshold; above a mean amplitude of 5 μV the value of the $\widehat{SD}$ goes to 1. The resulting expression for the

CRI is:

$$CRI = \widehat{SD}\left(\frac{\widehat{H_{Sh}} + \widehat{ADR} + \widehat{REG} + \widehat{COH}}{4}\right). \tag{7.8}$$

To evaluate the time dependency of the CRI, we introduce a "recovery function", $R(t)$, expressed as:

$$R(t) = a_0 + a_1 H(t-\delta)(1 - e^{-(t-\delta)/\tau}), \tag{7.9}$$

with H the Heaviside or step function. The constants a_0 and a_1, delay δ and time constant τ were estimated using the median values of the CRI, both for patients with good and poor neurological outcome.

Outcome Assessment

Neurological outcome assessment was performed at 3 and 6 months after cardiac arrest during a personal meeting or based on a telephone call, and was always performed by the same author (MT-C). The primary outcome measure was the best score within 6 months on the five-point Glasgow-Pittsburgh CPC scores[21]. Outcome was dichotomized between "good" and "poor". A good outcome was defined as a CPC score of 1 or 2 (no or moderate neurological disability), and a poor outcome as a CPC score of 3, 4, or 5 (severe disability, comatose, or death).

Statistical Analysis

Collected baseline characteristics include age, sex, weight, location of cardiac arrest (in-hospital vs. out-of-hospital), cause of cardiac arrest, and initial cardiac rhythm. Also information about the administered sedative (propofol and midazolam) and analgesic (fentanyl and remifentanyl) drugs and their maximum dose within the first 24 hours were collected. Statistical analysis for the variables that were categorical was performed using a Pearson chi-square test when no subgroup had an expected count less than 5, else a Fisher's exact test was performed. For continuous variables an independent t-test was applied after confirming that these variables were normally distributed.

At 12, 18, 24 and 36 hours after cardiac arrest, we determined the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Furthermore we defined at each of these time points two thresholds for the CRI score, one corresponding to a 100% specificity for predicting poor neurological outcome and one corresponding to a 100% specificity for predicting good neurological outcome. For each threshold we calculated the sensitivity, specificity,

positive predictive value (PPV) and negative predictive value (NPV), and their 95% confidence intervals (CI).

Results

In total 109 consecutive patients were included in the study. The first 56 patients were used as the training set and the remainder 53 patients were included in the test set. In the training set, 27 out of the 56 patients (48%) had good neurological outcome (best CPC score ≤2 within 6 months). In the test set, 26 out of the 53 patients (49%) had good neurological outcome. Additional patient information of the training set is given in[8]. Table 7.1 summarizes the patient characteristics of the test set. Both in the training and test set group, patients with good neurological outcome and patients with poor neurological outcome were sedated at same dosage levels. However, in the test group, patients with good neurological outcome received a slightly higher dose of propofol in comparison to patients with poor neurological outcome (Table 7.1).

Figures 7.4A and 7.4B show the median CRI values of patients with good and poor neurological outcome and their corresponding ranges. Figure 7.4A show the results of the training set and figure Figure 7.4B for the test set. In both the training and test set patients with good neurological outcome have an overall higher CRI than the group of patients with poor neurological outcome. We obtained a reasonable fit of the mean CRI values using the recovery function given by Equation 7.9. Note that the largest difference between the fitted recovery curves is present between 6 and 24 hours after cardiac arrest. The time constant τ is substantially larger in the patients with poor neurological outcome (τ=14.2 in the training set and τ=20.2 hours in the test set) in comparison to the patients with good neurological outcome (τ=6.4 in the training set and τ=4.5 hours in the test set), indicating that the EEG of patients with good neurological outcome shows a faster improvement.

Tables 7.2a and 7.2b show the results for predicting poor outcome at 12, 18, 24 and 36 hours after cardiac arrest. Table 7.2A shows the results for the training set and Table 7.2B for the test set. At 18 or 24 hours, the CRI performs best. At 24 hours after cardiac arrest, a CRI ≤0.29 was always associated with poor neurological outcome, with a sensitivity 0.55 (CI: 0.32–0.76) at a specificity of 1.00 (CI: 0.86–1.00) in the test set. This results in a PPV of 1.00 (CI: 0.73–1.00) and a NPV of 0.71 (CI: 0.53–0.85). At the same time point a CRI>0.69 can be used for predicting good outcome, with a sensitivity of 0.25 (CI: 0.10–

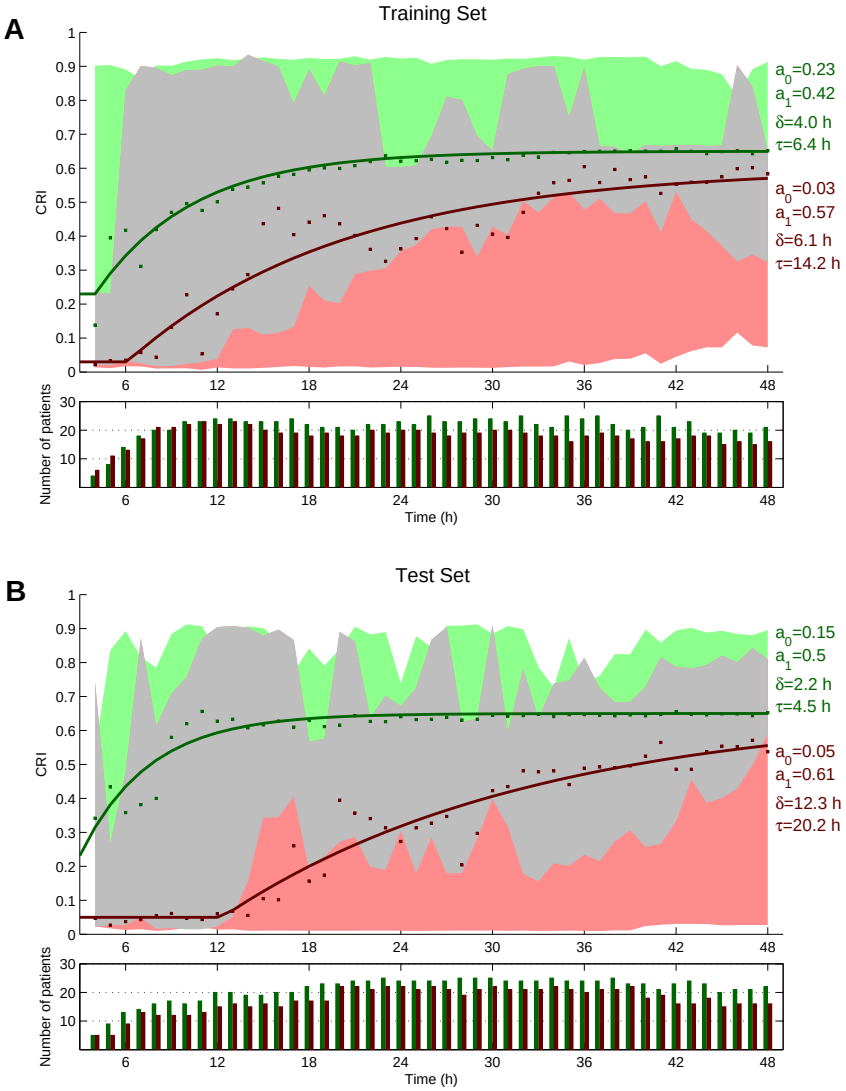

Figure 7.4: Values of the Cerebral Recovery Index (CRI) for the training (A) and test (B) set. The green and red dots are the median values for patients with good and poor neurological outcome at each time point, the green and red areas are the correspondig ranges. The grey area represents the area where the green and red areas overlap. The fitted recovery functions, $R(t)$ (Equation 7.9), are given as a solid line. Note that the largest difference between the fitted CRI curves is present between 12 and 24 hours after cardiac arrest.

Table 7.1: Comparison of patient characteristics between the patients with good neurological outcome and poor neurological outcome in the test set. Medication doses are given as the maximum drug dose during the first 24 hours. (CPC=Cerebral Performance Category, CA=Cardiac arrest)

	Poor neurological outcome (CPC 3–5)	Good neurological outcome (CPC 1–2)	*p*-value
Number of patients	27	26	-
Number of male	19 (70%)	20 (77%)	0.59
Age (years)	63 (std 13) (range: 27 to 82)	58 (std 11) (range: 35 to 79)	0.14
Number of OHCA	23 (85%)	23 (89%)	1.00
Initial Rhythm			0.00
VF	8 (30%)	23 (89%)	
Asystole	14 (52%)	0 (0%)	
Bradycardia	1 (4%)	0 (0%)	
Unknown	4 (15%)	3 (12%)	
Presumed cause of CA			0.57
Cardiac	17 (63%)	17 (65%)	
Other origin	6 (22%)	3 (12%)	
Unknown	4 (15%)	6 (23%)	
Patients sedated with propofol	27 (100%)	26 (100%)	-
Propofol dose (mg/h/kg)	2.8 (std 1.0) (range: 0.9 to 4.8)	3.4 (std 1.0) (range: 1.3 to 5.4)	0.03
Patients sedated with midazolam	8 (30%)	6 (23%)	0.59
Midazolam dose (μg/h/kg)	80 (std 65) (range: 30 to 214)	73 (std 35) (range: 33 to 125)	0.84
Patients treated with fentanyl	18 (67%)	19 (73%)	0.61
Fentanyl dose (μg/h/kg)	1.5 (std 0.8) (range: 0.6 to 3.6)	1.9 (std 0.7) (range: 0.9 to 2.7)	0.13
Patients treated with remifentanil	11 (41%)	7 (27%)	0.29
Remifentanil dose (μg/h/kg)	4.0 (std 2.6) (range: 1.0 to 7.0)	5.5 (std 3.0) (range: 3 to 11)	0.28

0.14) at a specificity of 1.00 (CI: 0.85–1.00) in the test set, and a corresponding NPV of 1.00 (CI: 0.54–1.00) and a PPV of 0.55 (CI: 0.38–0.70).

Discussion

There is growing evidence that EEG monitoring can play a significant role in the prediction of neurological outcome in patients treated with hypothermia after cardiac arrest[6–9]. In addition to prognostic parameters based on visual interpretation of the EEG, we introduce the “Cerebral Recovery Index” (CRI) based on five qEEG features that grades the EEG patterns as observed in

Table 7.2: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC) for predicting neurological outcome in the training set (A) and test set (B) at different time points after cardiac arrest. At each time points we selected two thresholds for the Cerebral Recovery Index (CRI), one corresponding to a 100% specificity for predicting poor neurological outcome and one corresponding to a 100% specificity for predicting good neurological outcome. In addition the 95% confidence intervals (CI) were given.

A: Training Set.

Time	AUC	CRI	Predicting	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)
12 h	0.83	<0.04	Poor outcome	0.27 (0.11–0.50)	1.00 (0.86–1.00)	1.00 (0.54–1.00)	0.60 (0.43–0.75)
		>0.90	Good outcome	0.13 (0.03–0.32)	1.00 (0.85–1.00)	1.00 (0.29–1.00)	0.51 (0.35–0.67)
18 h	0.69	<0.19	Poor outcome	0.28 (0.10–0.53)	1.00 (0.85–1.00)	1.00 (0.48–1.00)	0.63 (0.45–0.79)
		>0.91	Good outcome	0.05 (0.00–0.22)	1.00 (0.81–1.00)	1.00 (-)	0.46 (0.30–0.63)
24 h	0.87	<0.35	Poor outcome	0.45 (0.23–0.68)	1.00 (0.85–1.00)	1.00 (0.66–1.00)	0.68 (0.49–0.83)
		>0.61	Good outcome	0.57 (0.35–0.77)	1.00 (0.83–1.00)	1.00 (0.75–1.00)	0.67 (0.47–0.83)
36 h	0.74	<0.32	Poor outcome	0.28 (0.10–0.53)	1.00 (0.86–1.00)	1.00 (0.48–1.00)	0.65 (0.75–1.00)
		>0.91	Good outcome	0.04 (0.00–0.21)	1.00 (0.81–1.00)	1.00 (-)	0.44 (0.28–0.60)

B: Test Set.

Time	AUC	CRI	Predicting	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)
12 h	0.74	<0.02	Poor outcome	0.13 (0.02–0.40)	1.00 (0.83–1.00)	1.00 (0.16–1.00)	0.60 (0.42–0.77)
		>1.00	Good outcome	0.00 (0.00–0.17)	1.00 (0.78–1.00)	-	0.43 (0.26–0.60)
18 h	0.94	<0.18	Poor outcome	0.59 (0.33–0.82)	1.00 (0.85–1.00)	1.00 (0.69–1.00)	0.76 (0.56–0.90)
		>0.57	Good outcome	0.64 (0.41–0.83)	1.00 (0.80–1.00)	1.00 (0.77–1.00)	0.68 (0.46–0.85)
24 h	0.87	<0.29	Poor outcome	0.55 (0.32–0.76)	1.00 (0.86–1.00)	1.00 (0.73–1.00)	0.71 (0.53–0.85)
		>0.69	Good outcome	0.25 (0.10–0.47)	1.00 (0.85–1.00)	1.00 (0.54–1.00)	0.55 (0.38–0.70)
36 h	0.84	<0.22	Poor outcome	0.30 (0.12–0.54)	1.00 (0.86–1.00)	1.00 (0.54–1.00)	0.63 (0.46–0.78)
		>1.00	Good outcome	0.00 (0.00–0.14)	1.00 (0.83–1.00)	-	0.45 (0.30–0.61)

patients after cardiac arrest. This index may assist in the prediction of neurological outcome after cardiac arrest. The advantage of a combined qEEG feature is that it is very simple to use and trends in long term EEG recordings can easily be studied, while it still covers more than one aspect of the EEG. We evaluated the CRI in a training group of 56 patients and a test group of 53 patients treated with hypothermia at the ICU after cardiac arrest.

Although many features can be extracted from EEG data[11,13,18,22], only five were used in this study. The selection of features was motivated by the EEG characteristics that neurophysiologists evaluate in visual interpretation of EEG in patients after cardiac arrest. Subsequently, the features were combined into a single number: the Cerebral Recovery Index (CRI). For a proper evaluation of the CRI, we used an independent training and test set.

CRI scores are higher in patients with good outcome in comparison to patients with poor outcome and can be used to divide patients into three groups. The first group (green area in Figure 7.4) only includes patients with good neurological outcome: at 24 hours after cardiac arrest, 25% of the patients with good neurological outcome are in this group. The second group (red area in Figure 7.4) only includes patients with poor neurological outcome, at 24 hours after cardiac arrest, this group includes around 55% of all patients with poor neurological outcome. The last group (the grey area) in Figure 7.4) includes patients with good as well as with poor neurological outcome. The first and second group are of the most interest, since outcome prediction is 100% reliable in these patients.

The median values of the CRI of both groups of patients increased over time. However, the time constant in the recovery function $R(t)$ of patients with good neurological outcome is much smaller than in patients with poor neurological outcome. This implies that the EEGs of patients with good neurological outcome improve faster than those of patients with poor outcome. We also showed that the CRI at 18 and 24 hours after cardiac arrest has a higher prognostic value in comparison to the values at 12 or 36 hours after cardiac arrest. This is similar to the time course reported in our previous study using visual analyses[8]. Therefore, it is important to start the EEG registration within the first 24 hours after cardiac arrest for maximal diagnostic yield. The CRI threshold for the prediction of poor outcome with a 100% specificity increases from a value of 0.02 to 0.29 in the period 12-24 hours. This reflects the evolution in EEG

patterns, in agreement with visual inspection. For instance, an iso-electric EEG in the first hours after cardiac arrest is observed both in patients with a good and poor outcome[6,8]. Such an iso-electric EEG will have a very low CRI score of almost zero, since the feature for the amplitude is multiplied with the summed values of the other four features. In all patients with good neurological outcome, iso-electric EEG patterns, if initially present, will evolve within 24 hours to a burst-suppression or a continuous EEG pattern[8]. This is reflected by a CRI score of ¿0.69 at 24 hours. The interpretation of the EEG for prognostication, either quantitative with the CRI or with visual interpretation, must, therefore, be related to the time since cardiac arrest. We used 5 minute epochs of EEG with the least amount of artefacts every hour or every two hours to limit the influence of artefacts on the CRI score. As the EEG patterns of patients after cardiac arrest in general evolve over hours[8], this interval is sufficient to track relevant changes.

The thresholds for the CRI slightly varied between the training and test set. For predicting poor outcome at 24 hours the threshold decreased from 0.35 to 0.29, while for predicting good outcome at 24 hours the threshold increased from 0.61 to 0.69. A larger test set is necessary to evaluate the thresholds of the CRI before application in the clinical setting. Additional improvement might be the reduction of the irregularity in the border between the grey and green area (representing a 100% specificity for predicting good outcome) in Figure 4. Since changes in the EEG typically occur slowly and continuously over time, this border should be smoother. The peaks in the border between the green and grey area are therefore non-physiological. At some points in time the green and grey area even completely overlap. This was caused by high amplitude and high frequency muscle artefacts, resulting in erroneously high CRI values in some patients with poor outcome, illustrating that in some patients our automated selection of artifact free EEG epochs was not sufficiently accurate.

Our method is completely automated, including the selection artefact free data. However, the automatic selection of artefact free data is not perfect, yet. An expert is needed to verify that the selected EEG epoch is indeed artefact free to assure that the CRI value is reliable. Therefore, quantitative EEG analysis can reduce the time needed to review long-term EEG and make interpretation more objective. However, it is primarily aimed to assist in the interpretation instead of replacing the visual analysis of the EEG by an expert neurologist.

The EEG registrations were accessible for the treating physicians at the ICU to allow treatment of epileptiform discharges. This could potentially have influenced decision making. However, the local protocols about patient treatments were strictly followed. As presently the EEG of the first 24 hours is not included in the Dutch guidelines, these findings were never used in the decision making. An absent SSEP during normothermia was a reason to stop treatment according to current guidelines. Other findings to stop treatment included absence of both pupillary light and cornea reflexes at day three after cardiac arrest, or an iso-electric or low-voltage EEG at day three. In patients with a motor score >4, or in patients that showed clinical improvement, treatment was never stopped. The CRI values were calculated offline after inclusion of all patients, and were therefore not available for the treating physicians. The likelihood of a self-fulfilling prophecy is thus very small. Also, the dichotomisation of continuous variables using a threshold has its limitations[23]. A larger test set is necessary to evaluate the thresholds of the CRI before application in a clinical setting. Evaluation in a larger population may also result in change of thresholds, which could make it less suitable for decisions that require 100% accuracy. In clinical practise, therefore, in the interpretation of the CRI the difference of the index from threshold should also be taken into account. Another limitation might be that all patients were sedated during the hypothermic phase with propofol and in some cases additionally with midazolam in a low dose, which could have influenced the EEG registrations. However, both in this and our previous study[8], we showed that at group level patients with good neurological outcome and patients with poor neurological outcome were sedated at same dosage levels. In the test group described in this study, patients with good neurological outcome even received a slightly higher dose of propofol in comparison to patients with poor neurological outcome. Although propofol may have a neuroprotective effect, this has only been shown in in vitro and in vivo established experimental models of acute cerebral ischemia[24,25]. No clinical data exist that establish neuroprotection by propofol in humans[26–28]. In our study, the mean difference in propofol dosage between the group of poor and good neurological outcome is small. The main reason for the difference in propofol dosage used is probably that the postanoxic encephalopathy in patients with good neurological outcome was less severe, resulting in more muscle activity. Therefore, a higher dosage of propofol was needed to limit shivering. This might indicate that the temperature regulation is less affected in patients with good neurological outcome[29]. Furthermore the improvements in EEG patterns were already visible within the first 24 hours after cardiac

arrest, while patients were still treated with hypothermia and received sedative drugs. Therefore, it is very unlikely that the changes in EEG can be explained by the use of sedative drugs.

Conclusions

We introduce the Cerebral Recovery Index (CRI) to quantify and grade continuous EEG data of patients after cardiac arrest. The CRI can assist in prediction of both poor and good neurological outcome within 24 hours after cardiac arrest.

Acknowledgements

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Part III

Computational Modelling

Chapter 8

Generalized periodic discharges after acute cerebral ischemia: Reflection of selective synaptic failure?

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Abstract

Objective: Generalized periodic discharges (GPDs) can be observed in the electroencephalogram (EEG) of patients after acute cerebral ischemia and reflect pathological neuronal synchronization. Whether GPDs represent ictal activity, which can be treated with anti-epileptic drugs, or severe ischemic damage, in which treatment is futile, is unknown. We hypothesize that GPDs result from selective ischemic damage of glutamatergic synapses, which are known to be relatively vulnerable to effects of ischemia.

Methods: We employed a macroscopic model of cortical dynamics in which we increasingly eliminated glutamatergic synapses. We compared the output of the model with clinical EEG recordings in patients showing GPDs after cardiac arrest.

Results: Selective elimination of glutamatergic synapses from pyramidal cells to inhibitory interneurons led to simulated GPDs whose waveshape and frequency matched those of patients showing GPDs after cardiac arrest. Mere reduction of glutamatergic synapses between pyramidal cells themselves did not result in GPDs.

Conclusion: Selective ischemic damage of glutamatergic synapses on inhibitory cortical interneurons leads to the generation of ischemia induced GPDs. Disinhibition of cortical pyramidal neurons is a candidate mechanism.

Significance: This study increases the insight in the pathophysiological mechanisms underlying the generation of GPDs after acute cerebral ischemia.

Introduction

Generalized period discharges (GPDs) are frequently encountered during electroencephalography (EEG) monitoring in comatose patients after cardiac arrest. GPDs are defined as synchronous bihemispheric, repetitive discharges of similar morphology with quantifiable, nearly regular, interdischarge intervals[1–4]. GPDs reflect pathological neuronal synchronization and are often associated with seizure activity[3,5]. However, it is unclear whether GPDs after ischemia are a true form of ictal activity[5,6]. In some literature prolonged periods (>30 min) of GPDs in comatose patient are interpreted as a form of (non-convulsive) status epilepticus[7,8]. No standard of care exists in these patients, since it is unknown whether early and aggressive treatment of comatose patients showing GPDs after ischemia improves outcome[5,6,8,9]. Most of these patients have poor outcome, with death in most cases and persistent vegetative state in few survivors[7,8]. GPDs therefore might rather be an expression of severe (often irreversible) ischemic damage, in which treatment is futile[5,10,11]. However, some examples of patients with good outcome after treatment with anti-epileptic drugs exist[12]. Better understanding of the pathophysiological processes leading to ischemia induced GPDs may clarify why some patients respond to treatment, but most of them do not.

Failure of synaptic transmission is an early consequence of cerebral ischemia and is reflected by changes in the EEG[13–16]. Although initially reversible, irreversible synaptic damage may occur if blood flow is not restored promptly[16]. Experimental studies in rat hippocampal slices showed that glutamatergic synapses are more vulnerable to ischemia than GABAergic[17]. This selective ischemic vulnerability of glutamatergic synapses to inhibitory, GABAergic, interneurons first leads to elimination of inhibitory cortical input[17–19].

Here we study the effect of selective ischemic synaptic damage on EEG patterns, with an established macroscopic computational model[20]. The model's output is the membrane potential of cortical pyramidal neurons, averaged over a macrocolumn. Thereby, the model provides a natural link with the EEG, which reflects currents within pyramidal apical dendrites, averaged over small pieces of cortical tissue[21–23]. This model has contributed to the understanding of diverse EEG phenomena, such as spontaneous rhythms, epileptic seizures, and anesthesia-induced changes[24–29].

We hypothesize that selective ischemic damage of glutamatergic synaptic input to inhibitory interneurons results in pathological neuronal synchronization, reflected as GPDs on the EEG. To test this hypothesis we study increasing elimination of these connections on simulated EEG patterns in our computational model. We discuss the implications of our results with regard to the pathophysiological mechanism leading to GPDs, including the presumed effect of treatment with anti-epileptic drugs.

Methods

Clinical data

We selected EEG recordings showing GPDs from a previously published prospective cohort study on the prognostic value of continuous EEG registrations in 56 comatose patients treated with hypothermia after acute global cerebral ischemia resulting from cardiac arrest[30].

EEGs were measured in one of the two intensive care units of the Medisch Spectrum Twente hospital (Enschede, The Netherlands) using 21 silver–silverchloride cup electrodes placed on the scalp according to the international 10–20 system. Recordings were made using a Neurocenter EEG recording system (Clinical Science Systems, Voorschoten, The Netherlands). All signals were filtered by a zero-phase 6th order Butterworth bandpass filter from 0.5 to 30 Hz. EEGs were independently described by two authors (MT-C and MvP). In case of disagreement, the final classification was decided by consensus. GPDs were defined as any pattern of synchronous, bilateral, repetitive discharges of similar morphology with nearly regular interdischarge intervals[3,4]. Besides EEG, in all patients daily somatosensory evoked potential (SSEP) recordings were made after bilateral electrical stimulation of median nerve using a Nicolet Bravo system (Viasys, Houten, The Netherlands).

Modeling cortical dynamics and synaptic failure

We employ the computational model of cerebral dynamics described in Liley et al.[20]. The model comprises the two major neuron types found in cortical tissue: pyramidal neurons and inhibitory interneurons. Both neuron types receive input via intra-cortical synaptic projections as well as non-specific excitatory input from regions not explicitly incorporated into the model, such as the thalamus. This synaptic organization is illustrated in Figure 8.1(a) and (b). Pyramidal neurons excite both themselves and inhibitory interneurons through glutamate-mediated synapses. Interneurons inhibit both themselves

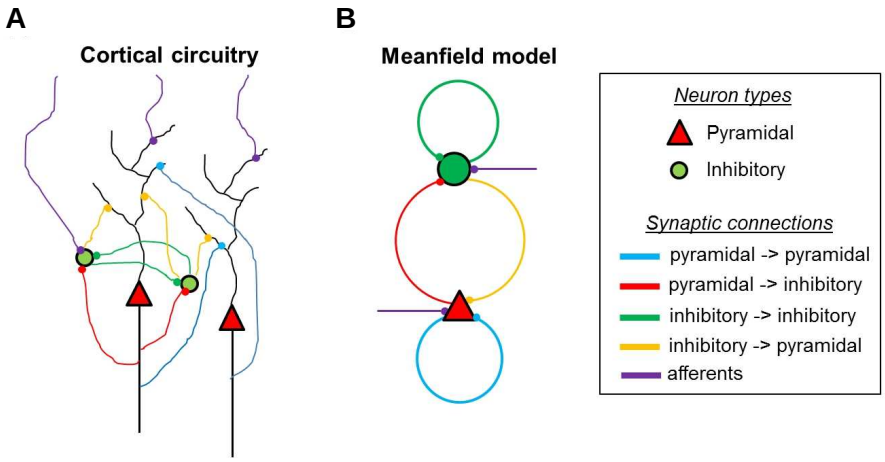

Figure 8.1: Structure of the cortical meanfield model. A, The model comprises pyramidal and inhibitory neurons with their respective local synaptic projections, as well as thalamic afferents. B, The meanfield model reduces the microscopic cortical circuitry to variables averaged over a macrocolumn, resulting in mean neuron types and mean synaptic projections.

and pyramidal neurons through GABA-mediated synapses. The EEG signal is modeled by the mean membrane potential of the pyramidal neurons, which are known to be approximately proportional to each other[20]. At baseline, we choose the model parameters as in Liley et al.[20], for which the simulated EEG displays alpha oscillations. The model equations and baseline parameters are given in Appendix A.

To model ischemia-induced glutamatergic synaptic damage, we increasingly reduced the number of functioning glutamatergic synapses. These excitatory glutamatergic synapses connect the pyramidal cells with the inhibitory interneurons as well as with the excitatory pyramidal cells themselves. A differential vulnerability between these two collections of synapses is incorporated into the model by independently reducing the number of synapses from excitatory pyramidal cells to inhibitory interneurons (N_{ei}) and the number of synapses between excitatory pyramidal cells (N_{ee}). The simulated EEG signals were classified into normal activity, GPDs or low voltage. In this classification of simulated EEG data, GPDs were defined similar as for the clinical registrations, with an additional requirement of an amplitude above 10 mV. The simulated EEG was classified as low voltage when the complete signal was below 0.25 mV. We visually compared the simulated EEGs with the clinical EEGs with regard to waveshape (duration and steepness) and frequency.

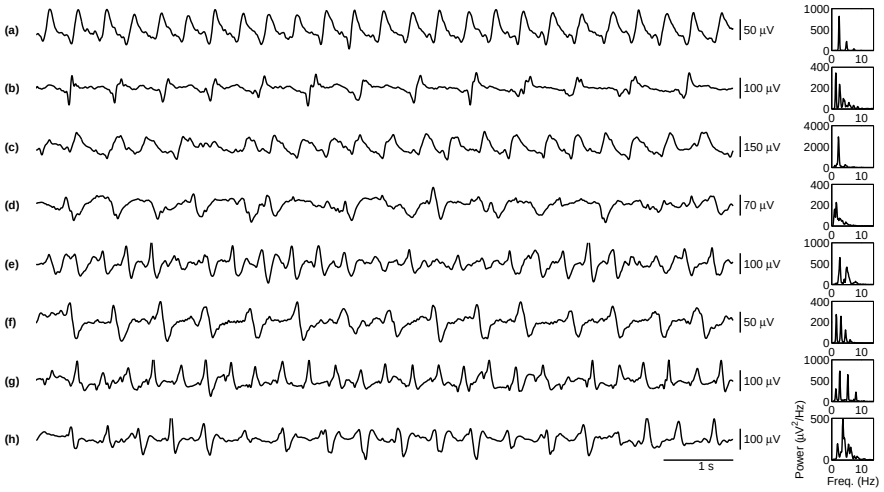

Figure 8.2: Generalized periodic discharges measured in eight comatose patients (a–h) after acute global cerebral ischemia due to cardiac arrest (left) with corresponding power spectra (right). The dominant frequency ranges from 1 to 3 Hz.

To test the stability of our results we varied three of the other parameters in the model and studied the effect on our results. We varied the standard deviation of non-specific fluctuations to excitatory cells (σ_{ne}^{p}) in a range of 90–110% of the original value. The spike thresholds (V_e^{spike} V_i^{spike}) were varied in a range of 95–105% of their original values.

8

Results

Clinical data

GPDs were seen in eight patients (14%, Figure 8.2). In all patients the early cortical (N20) SSEP response was preserved.

Model

The model generates an alpha rhythm when all synapses are intact (Figure 8.3). If N_{ee} is kept unchanged at 100%, a decrease of N_{ei} to 96–63% results in GPDs in the simulated EEGs. Lower N_{ei} results in GPDs with a higher frequency. Reducing N_{ei} below 63% rapidly results in complete depression of simulated cortical activity. Mere reduction of N_{ee} does not result in GPDs.

A 2D diagram were N_{ei} is varied along the x-axis and N_{ee} is varied along the y-axis is presented in Figure 8.4. This shows that the simulated EEG pattern is

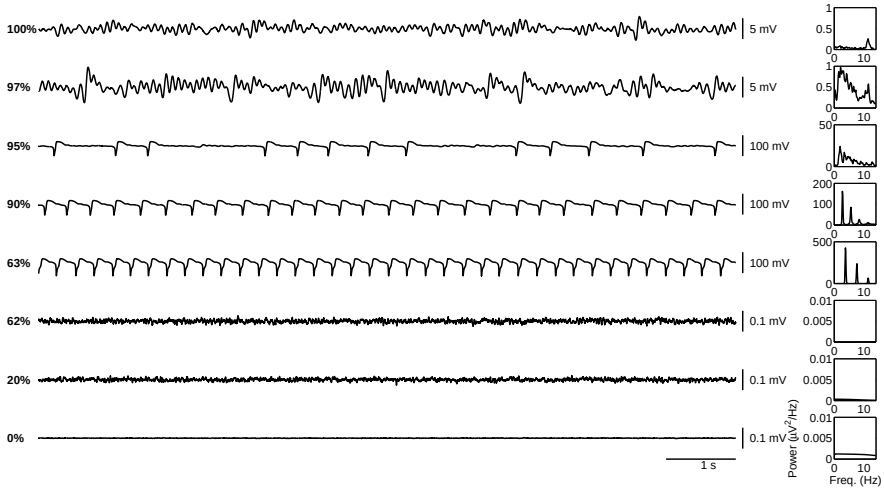

Figure 8.3: Examples of simulated EEG patterns obtained after gradually reducing the number of glutamatergic synapses from pyramidal cells to inhibitory interneurons (N_{ei}). All other parameters, including the number of glutamatergic synapses between pyramidal cells (N_{ee}), were unaffected. If N_{ei}=100%, the model shows alpha activity (top). If 63%≤N_{ei}≤96%, the model shows GPDs. If this number is further reduced, the activity rapidly reduces to a very low amplitude signal (bottom).

dependent on the ratio between N_{ei} and N_{ee}, where GPDs, can only be present if N_{ei} is lower (more affected) than N_{ee}.

Simulated and clinical GPDs show similar sharp periodic discharges with faster, low-amplitude activity in between (Figure 8.5). The power spectra of both signals have similar peak frequencies, with a dominant frequency of 1–3 Hz. However, the clinical EEG signals with GPDs show more variability of peaks and have less sharp negative deflections than the simulated ones.

Variation of the non-specific fluctuations to excitatory cells (σ^p_{ne}) in a range of 90–110% of the original value did not have any effect on the results. Variation of the spike thresholds (V_e^{spike} and V_i^{spike}) in a range of 95–105% of their original values caused a shift in the borders of Figure 8.4 between the areas corresponding to GPDs, normal EEG and low amplitude EEG. However the same patterns were still seen.

Dynamical systems theory allows a characterization of the type of activity in each of the EEG regimes observed in Figure 8.4, as well as of the type of transi-

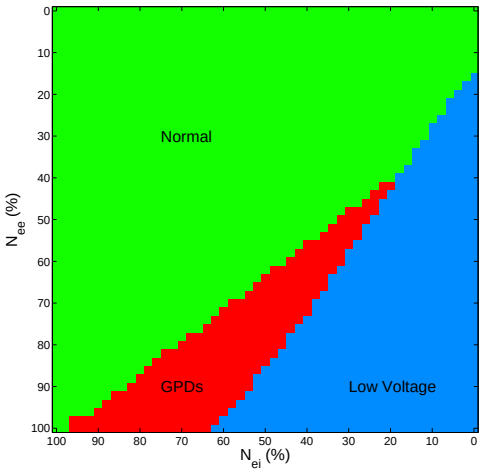

Figure 8.4: Diagram of simulated EEG patterns obtained after gradually reducing the number of glutamatergic synapses from pyramidal cells to interneurons (N_{ei}) and the number of glutamatergic synapses between pyramidal cells (N_{ee}). Note that it must hold that $N_{ei}<N_{ee}$ to generate GPDs (red area). A further decrease in N_{ei} leads to the generation of low voltage EEG patterns (blue area), while normal EEG patterns are generated when $N_{ei}\geq N_{ee}$ (green area).

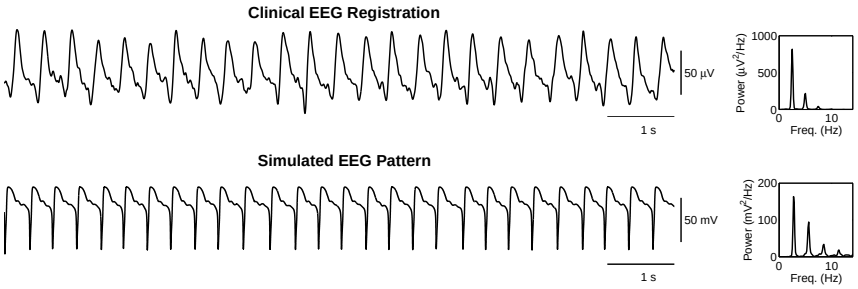

Figure 8.5: Top: EEG recording from a patient after cardiac arrest showing generalized periodic discharges (GPDs). Bottom: simulated EEG showing GPDs. In this simulation the number of synapses from pyramidal cells to interneurons (N_{ei}) was reduced to 90%, while the number of synapses between pyramidal cells (N_{ee}) was 100%.

tions through which the cortical column switches between these regimes[31,32]. Although a formal mathematical analysis is outside the scope of the present study, we provide an intuitive description obtained using numerical simulations of the model equations. Both the baseline (green area) and the low-voltage EEG (blue area) correspond to spontaneous fluctuations around a stable equilibrium voltage. This means that the EEG activity in these regimes

is not intrinsically generated within the cortical column, but is driven by stochastic subcortical activity impinging on cortical pyramidal neurons (see Figure 8.1). However, while in baseline EEG, these fluctuations have a characteristic frequency and correspond to physiological alpha activity[20], the low-voltage fluctuations are absent of oscillations, indicating pathological activity. The transition from low-voltage EEG to GPDs (red area) corresponds to a subcritical Hopf bifurcation, meaning that GPDs arise suddenly out of the low-voltage activity (see Figure 8.3, fifth and sixth row). In contrast, in baseline EEG and in the neighborhood of the GPD regime, spontaneously occurring GPDs can be observed (see Figure 8.3, second and third row), indicating bistable dynamics. The transition from baseline EEG to GPDs corresponds to a saddle-node bifurcation after which GPDs coexist with small-amplitude limit-cycles in the alpha frequency range. While clearly visible in the second trace of Figure 8.3, these alpha oscillations are barely observable in the GPD regime since their amplitude is about 20 times smaller than the amplitude of the GPDs. Interestingly, in the EEG traces of some patients, small-amplitude alpha oscillations can indeed be observed (see Figure 8.2(a) and (f)).

Pathophysiological mechanisms

In this section we describe the electrophysiological mechanisms that are suggested by the model to underlie the generation of ischemia-induced GPDs. Figure 8.6(a) shows the average membrane voltage of the population of pyramidal neurons during one cycle of the GPDs. To get a clear view of the dynamics, we also plotted the currents entering the population of pyramidal neurons. Specifically, we show the passive membrane current (green line), the net synaptic current (blue line), and the total current (red line) of this population. Note that the net synaptic current is comprised of the current due to axonal projections from the inhibitory population and from the pyramidal population itself. In this simulation, we set the afferent inputs to the cortical column to zero, so the total current is the sum of the membrane currents and synaptic currents only. A first observation is that GPDs can be generated within cortical tissue even in the absence of non-specific afferents. In particular, since the dynamics of the pyramidal voltage is not driven by afferent fluctuations, GPDs are self-sustained and autonomously generated within local cortical tissue.

Figure 8.6(b) schematically depicts the chain of events taking place in the modeled cortical column during one cycle of the GPDs. Starting at the resting membrane voltage, the loss of excitation of cortical interneurons due to selective ischemia-induced synaptic failure leads to disinhibition of pyramidal

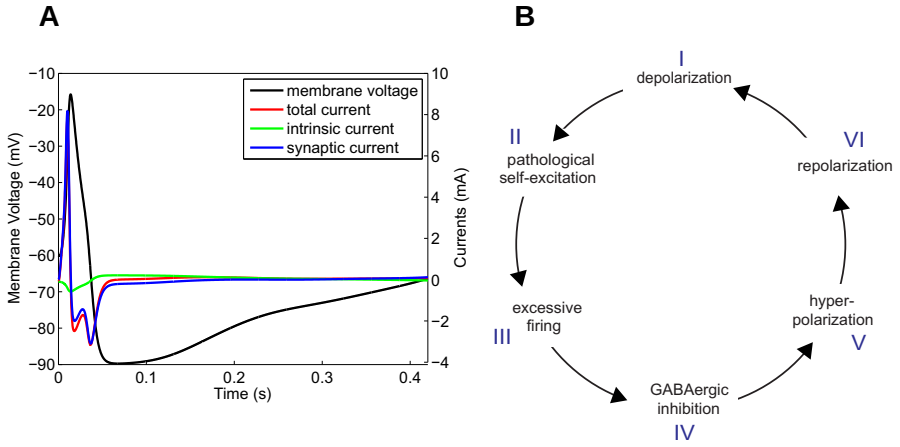

Figure 8.6: Putative physiological mechanisms underlying the generation of ischemia-induced GPDs. A, Mean membrane voltage of the pyramidal population (black line), together with the intrinsic (green line), synaptic (blue line), and total current (red line) arriving at the cell bodies during one period of the GPDs. In the simulations we used the baseline parameter values except we set the afferent inputs to the cortical column to zero ($p_{ne}=p_{ni}=\sigma^p_{ek}=\sigma^p_{ik}=0$). Since these parameter changes shifted the threshold for GPDs generation from $N_{ei}\approx96\%$ to $N_{ei}\approx105\%$, we set $N_{ei}=100\%$. B, Chain of events taking place in the modeled cortical column during one cycle of the GPDs.

neurons and therefore to higher excitation of interneurons. However, since GABAergic synapses act faster than glutamatergic (or AMPAergic) synapses this initially results in a gradual depolarization of the pyramidal neurons (I). When the depolarization is large enough, the non-linear activation properties of the pyramidal neurons lead to pathological self-excitation (II), resulting in excessive firing-rates (III). This is reflected in the membrane voltage by a high peak. Due to a changing balance between excitation and inhibition of the pyramidal neurons (IV), which can be seen by the steep decrease in incoming synaptic current, the pyramidal neurons are rapidly hyperpolarized (V), which leads to the near absence of firing in the cortical column. This is reflected in the pyramidal membrane voltage by a deep trough, close to the reversal potential of chloride, which is about –90 mV. Since inhibition has now worn off, the passive membrane current leads to a gradual repolarization of the membrane potential (VI) until it reaches the resting membrane voltage from where the cycle repeats itself.

Discussion

In this meanfield model of cortical dynamics we show that selective reduction of excitatory (glutamatergic) input to inhibitory cortical interneurons leads to GPDs. The frequencies and shapes of the waveform of the simulated GPD patterns qualitatively matched those of GPDs in patients after acute cerebral ischemia. Further reduction of the number of glutamatergic synapses to inhibitory interneurons rapidly resulted in low-voltage EEGs, which are regularly encountered in these patients[30,33,34]. Mere reduction of glutamatergic synapses to excitatory pyramidal cells did not result in GPDs.

Our findings support the hypothesis that GPDs after cerebral ischemia may result from selective ischemic damage of excitatory synapses on inhibitory interneurons. The modeling carried out in this study suggests that this selective synaptic failure leads to the emergence of GPDs via a disinhibition of pyramidal neurons. This finding that networks with weakened or reduced excitatory synapses can lead to epileptiform activity was described previously in a computational model and confirmed in an experimental study in neocortical slices of mice[35]. This idea of reduction of excitatory activity as a possible pathway for epileptiform activity is in contrast with the general thought that epileptiform activity is caused by an increased excitation or decreased inhibition. The notion of excitation as a remedy against epileptiform activity has been supported by a case report on an 11-year old patient with idiopathic childhood occipital epilepsy of Gastaut. In this patient various additional stimuli suppressed epileptiform discharges[36].

High ischemic vulnerability of glutamatergic relative to GABAergic synapses has been demonstrated previously in vitro: in rat hippocampal slices, anoxia affected evoked excitatory more than inhibitory postsynaptic currents[16,17,19]. Even more specifically, anoxia particularly affected excitatory input to inhibitory cortical interneurons, leading to elimination of inhibitory cortical input[17]. However, this study was performed in slices of the CA1 region of rat hippocampus. Whether this also applies to the interneurons in the cortex is unknown. Moreover there are several types of cortical interneurons with different types of synaptic connections. Therefore, our model represents a simplification of only part of the complex network dynamics in the cortex presumably playing a role in the generation of GPDs.

As reduced glutamatergic input to inhibitory interneurons results in an overall increase in excitation of cortical networks, the proposed mechanism suggests

that the network mechanisms underlying the generation of GPDs are similar to those involved in the generation of certain types of seizure activity. This is supported by the strong association between GPDs and non-convulsive seizure activity: in more than 25% of patients with GPDs, non-convulsive seizures or status epilepticus is diagnosed[3].

GPDs are not only observed in patients after cerebral ischemia. Other conditions include acute brain injury, acute systemic illness, metabolic disorders and epilepsy[3,7]. It is unclear, if selective synaptic failure is present in these patients too. However, in these conditions mitochondrial function is supposed to be affected[37,38], and selective synaptic dysfunction of glutamatergic synapses due to energy depletion is then indeed a candidate mechanism.

The meanfield model used in this study provides a direct link with the EEG. In our study, the frequency and shape of GPD waveforms were qualitatively similar to those from patients after cardiac arrest. However, there were some morphological differences in the time-series. A partial explanation could be a lack of spatial conduction effects in the model's time-series[20,39], which unfortunately can not be studied in this simplified meanfield model. Investigation of this issue requires the use of the full spatio-temporal model in combination with a forward model of the EEG[40]. Second, a global parameter search for GPDs within the currently used model could lead to GPDs with varying waveforms. Such a search has been performed using the full spatio-temporal model in the context of modeling the effect of anesthetic agents[27].

In patients after cardiac arrest GPDs are typically observed over large parts of the cortex and are bilateral synchronous[1–3]. One of the limitations of this model is that we cannot explain this aspect of GPDs. To study GPDs recorded from different electrodes, the use of a full spatio-temporal model of the human cortex is needed[20,41,42]. Alternatively, synchronization between GPDs recorded from various cortical regions could be mediated through thalamocortical feedback loops, which are known to be involved in the generation of both physiological and pathological rhythms in the brain[43] and could be studied in a thalamocortical model[44]. The contribution of such a thalamocortical loop in the synchronization of GPDs indeed remains possible as in our study all eight patients showing GPDs had preserved early cortical SSEP responses, suggesting that the thalamocortical loop in these patients was still, at least partially, intact[45]. However, the meanfield model we use does not contain

such a thalamocortical loop. Therefore the effect of the thalamocortical loop on synchronization of GPDs cannot be studied using this model.

Depression of glutamatergic synapses may also affect the early cortical SSEP response: the N20 is generated in the primary somatosensory cortex[46,47] and its presence depends on an intact functioning of the thalamocortical glutamatergic synapses on pyramidal cells in area 3B[45,48]. Most likely, however, these synapses are relatively resistant to hypoxic incidents as in some patients preserved early SSEPs were recorded while the EEG was essentially isoelectric[45]. Our current clinical data support the hypothesis that the glutamatergic thalamocortical synapses are more resistant to hypoxic incidents than the intracortical glutamatergic synapses (N_{ei}), as in all our patients SSEPs (N20) were preserved, as well. However, to simulate changes in morphology of the early (N20) or late (>20 ms) SSEP components, would require further detailed modeling of cortical architecture, including the differential functional dependence of relevant synapses on ATP depletion. This falls outside the scope of the current contribution.

Ischemic synaptic damage is initially located presynaptically and is associated with impaired transmitter release[14,49]. Post-synaptic receptors are still functioning at that time. This explains why treatment with anti-epileptic drugs can result in a suppression of GPDs. If the presynaptic damage is irreversible, GPDs may recur after withdrawal of treatment, which is indeed often observed.

In conclusion, after cerebral ischemia, GPDs probably result from highly selective synaptic damage of glutamatergic synapses of excitatory pyramidal cells on inhibitory cortical interneurons. Disinhibition of cortical pyramidal neurons is a likely mechanism. Since this selective damage is likely irreversible, it may explain why treatment of GPDs with anti-epileptic drugs appears futile in most patients.

Acknowledgements

The authors would like to thank Dr. Hil Meijer for his assistance on the bifurcation analysis.

Appendix A: Model equations and baseline values

In this section we give a short mathematical description of the computational model of localized cortical dynamics employed in this study[20]. The model describes the dynamics of the average membrane potentials of a cortical macrocolumn comprised of pyramidal neurons and interneurons. Below, the indices e and i refer to pyramidal- and interneurons, respectively. The membrane potentials are denoted by $V_k(t)$ for $k{=}e,i$. Their dynamics are governed by the following set of differential equations

$$\tau_e \frac{dV_e}{dt} = V_e^{\text{rest}} - V_e(t) + \Psi^e_{\text{AMPA}} I_{ee}(t) + \Psi^e_{\text{GABA}} I_{ie}(t) + \Psi^e_{\text{AMPA}} I_{ne}(t), \tag{8.A.1}$$

$$\tau_i \frac{dV_i}{dt} = V_i^{\text{rest}} - V_i(t) + \Psi^i_{\text{AMPA}} I_{ei}(t) + \Psi^i_{\text{GABA}} I_{ii}(t) + \Psi^i_{\text{AMPA}} I_{ni}(t), \tag{8.A.2}$$

where τ_k and V_k^{r}, respectively, denote the membrane time-constants and resting-potentials and I_{kl} is proportional to the current flowing into population l due to activity of population k. The currents I_{ne} and I_{ni} model the afferent non-specific input to the cortical column and are modeled as uncorrelated white-noise processes with mean values p_{ne} and p_{ni} and standard-deviations σ^p_{ne} and σ^p_{ni}.

The currents I_{kl} are given by

$$I_{kl}(t) = h_{\text{GABA}} \otimes N_{kl} S_k(V_k(t)), \tag{8.A.3}$$

where

$$h_{\text{GABA}}(t) = t H_{\text{GABA}} \gamma_{\text{GABA}} \exp(1 - \gamma_{\text{GABA}} t) \tag{8.A.4}$$

is the response function of GABAergic receptors located on the dendrites of neurons within population l, which has rate-constant γ_{GABA} and efficacy H_{GABA} and similarly for AMPAergic responses. The parameter N_{kl} denotes the number of synaptic contacts on population l from axonal projections of population k. The function S_k relates the membrane potential of population k to its firing-rate and is given by

$$S_k(V_k) = \frac{Q_k^{\max}}{1 + e^{-\sqrt{2}(V_k - V_k^{\text{spike}})/\sigma_k}}, \tag{8.A.5}$$

Table 8.A.1: Model parameters, their symbols, and baseline values. The index k refers to neural population of type k=e, i.

Parameter	Symbol	Baseline value
Maximum spike-rate	$Q_k^{\max}$	500 s^{-1}
Spike-thresholds	V_k^{spike}	–50 mV
Standard deviation of spike-thresholds	σ_k	5 mV
Synaptic efficacies	$H_{\text{GABA}}, H_{\text{AMPA}}$	0.71 mV
Reversal potentials	$E_{\text{GABA}}, E_{\text{AMPA}}$	–90, 40 mV
Number of synaptic contacts from k to l	$N_{ei}, N_{ee}, N_{ie}, N_{ii}$	3000, 3000, 500, 500
Membrane time-constants	τ_e, τ_i	0.094, 0.042 s^{-1}
Resting potentials	V_k^{rest}	–70 mV
Synaptic rate-constants	$\gamma_{\text{GABA}}, \gamma_{\text{AMPA}}$	65, 300 s^{-1}
Non-specific firing-rates	p_{ne}, p_{ni}	3460, 5070 s^{-1}
Standard deviation of non-specific fluctuations	$\sigma_{ne}^p, \sigma_{ni}^p$	1000, 0 s^{-1}

where $Q_k^{\max}$ and V_k^{spike} denote, respectively, the maximal firing-rate and spike-threshold of population k and σ_k denotes the standard-deviation of spike-thresholds over population k.

The variables Ψ^k_{AMPA} and Ψ^k_{GABA} are dimensionless and model the dependence of AMPAergic and GABAergic synaptic conductance on the membrane potential of the post-synaptic neural population k. They are given by

$$\Psi^k_{\text{AMPA}}(V_k) = \frac{E_{\text{AMPA}} - V_k}{|E_{\text{AMPA}} - V_k^{\text{r}}|}, \tag{8.A.6}$$

where E_{AMPA} denotes the reversal-potential of this receptors type, and similarly for GABAergic synaptic transmission. The baseline values for all model parameters were taken from[20] and are listed in Table 8.A.1.

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Chapter 9

General Discussion

In 50–60% of patients treated with therapeutic hypothermia after cardiac arrest, consciousness never returns[1,2]. Early identification of patients with poor neurological outcome can prevent continuation of futile medical treatment, decreases ICU stay and medical costs, and shortens the time of uncertainty for the patient's family. Early and reliable prognostication is therefore highly relevant. However, neurological evaluation is limited in patients treated with hypothermia. Several studies showed that the use of clinical and biochemical parameters, such as the motor score, have become unreliable as prognostic parameters since the introduction of therapeutic hypothermia[3–8]. Imaging methods only visualize structural damage, while functional failure is not assessed. The EEG directly measures the spontaneous electrical activity of the brain through the skull and reflects the functioning of cortical synapses[9], which is the process that is the most sensitive for ischemia[10].

A new application of an old method

The EEG is a very old measurement tool. In 1924, Hans Berger already recorded the first human EEG on his son[11,12]. So why is the EEG until now not routinely used in patients after cardiac arrest? Before the introduction of hypothermia in 2002 as a treatment for comatose patients after cardiac arrest[13,14], patients received no sedation and clinical parameters were reliable for the prediction of poor neurological outcome[15]. The need for other parameters for outcome prediction, therefore, strongly increased since the introduction of hypothermia. While most clinical and biochemical markers become unreliable, we show that the EEG during hypothermia can still reflect the neurological status of the patient and predicts neurological outcome at an early stage. Within the period of hypothermia the patterns that can be observed in patients with both poor and good outcome show characteristic evolutions. The prognostic

value of these EEG changes is critically dependent on the time since cardiac arrest. Therefore, this evolution can only be observed when the right points in time are monitored, preferably with continuous EEG registrations.

Effect of hypothermia and sedation on the EEG

Although hypothermia can affect the EEG at temperatures below 30°C, the effect of mild hypothermia (33°C) on the EEG is relatively small, with only small shifts in frequencies[16,17]. The EEG changes to a burst suppression pattern around 25°C and electrocerebral silence appears around 18°C[17]. Also, the use of anaesthetics can influence the EEG, however these influences are well known. In the relatively low dosages that were used in our patients, the EEG remains continuous, with anteriorization of the alpha rhythm[18,19]. Patterns we found to be associated with poor outcome cannot be solely drug induced in our patients.

EEG rhythms in postanoxic coma

While measuring the EEG in patients after cardiac arrest, a rich variety in rhythms can be observed that evolve over time. Patients with good outcome can initially show iso-electric EEGs or low-voltage EEG patterns, which recover relatively fast within the period of hypothermia to a burst-suppression or a continuous pattern. This improvement in EEG rhythms in patients with good outcome is most likely a reflection of synapses which recover from reversible damage. Other patients with good neurological outcome almost immediately show a continuous EEG pattern with relatively fast frequencies. Patients with poor outcome show initially iso-electric patterns, low voltage or burst-suppression patterns. Their EEGs do not improve at all, or at a much slower timescale in comparison to patients with good outcome. The rate of improvement is therefore very important for the outcome and presumably reflects the reversibility of the cortical damage. Some patients with poor outcome even show deterioration of their EEG patterns, which might reflect secondary ischemic injury including cell swelling and cell death.

A first classification of the EEG background pattern and the evolution over time is highly relevant for the prediction of neurological outcome in patients after cardiac arrest. Therefore, the analysis of continuous EEG measurements should be focused on the *evolution* in EEG background patterns. This requires a different and less intensive approach of visual analysis in comparison to the

visual analysis of a 20 min routine recording in which each page of 10 seconds of EEG is extensively reviewed.

Prediction of poor neurological outcome

In our first cohort study of 60 patients, described in Chapter 2, we showed that EEGs with an iso-electric or low-voltage pattern at 24 hours after cardiac arrest reliably predict poor neurological outcome with a sensitivity of 40% and a 100% specificity. In contrast, the sensitivity for bilateral absence of the SSEP was only 24%. Also, burst-suppression patterns at 24 hours were associated with poor neurological outcome, but not inevitably so, since some of the patients with good neurological outcome had a burst suppression pattern at 24 hours after cardiac arrest. However, we discovered that many different types of burst-suppression patterns exist and that a subclassification of burst-suppression patterns might be useful. In Chapter 3 we show that "burst-suppression with identical bursts" is a distinct pathological EEG pattern in which shapes of subsequent bursts are identical. Burst-suppression with identical bursts was in our series only observed in patients after diffuse cerebral ischemia and was inevitably associated with poor outcome.

To test our findings that EEGs with iso-electric patterns, low voltage patterns or burst-suppression patterns with identical bursts at 24 hours after cardiac arrest are associated with poor neurological outcome, we evaluated a larger cohort of 148 patients. The results are given in Chapter 4. We found that this combined group of severe EEG patterns at 24 hours after cardiac arrest is associated with poor neurological outcome with a sensitivity of 48% and a specificity of 100%.

Prediction of good neurological outcome

The EEG can be used for the prediction of good neurological outcome as well. In the first group of 60 patients (Chapter 2), we found that at 12 hours after resuscitation, 43% of the patients with good neurological outcome showed continuous, diffuse slowed EEG rhythms, while non of the patients with poor neurological outcome showed one of these rhythms within 12 hours after cardiac arrest. In the larger group of patients described in Chapter 4 we still found that normal or diffuse slowed EEG patterns at 12 hours after cardiac arrest are associated with good neurological outcome with a sensitivity of 57%. Unfortunately, there where two patients with poor neurological outcome showing a diffuse slowed EEG pattern at 12 hours after cardiac arrest, resulting in a specificity of 96%. However, both patients died because from cardiac problems and not from postanoxic encephalopathy.

Self-fulling prophecy

A problem in all unblinded studies on the prediction of neurological outcome is the so called "self-fulfilling prophecy"[20–22]. In an ideal study the treating physicians are completely blinded to all EEG and SSEP registrations and treatment should not be limited or withdrawn in any patient included in the study. However, this is considered as unethical. In our study, the treating physicians were not completely blinded to the EEG and SSEP registrations, which may have influenced the clinical decision making. Standard guidelines on patients treatment, including guidelines on the continuation of treatment, were strictly followed. According to these guidelines, the EEG at 24 hours was not used for treatment decisions. Furthermore, visual classification of the EEG patterns was performed offline. Therefore the likelihood of a self-fulfilling prophecy is expected to be very small.

Treatment of electroencephalographic status epilepticus

The increased use of EEG monitoring leads to an increased detection of electroencephalographic seizures and status epilepticus. However, it is currently unknown whether these patterns reflect epileptic activity that can be treated with anti-epileptic drugs to improve patients' outcome, or rather severe ischemic damage, in which treatment is futile[23–27]. In Chapter 5 we showed in a retrospective study that moderate treatment with anti-epileptic drugs does not improve outcome of patients with electroencephalographic status epilepticus after cardiac arrest. Since no strict treatment guidelines existed for epileptiform activity in these patients, both the nature and the intensity of treatment varied among physicians, however treatment was mostly moderate started at at a median of 47 hours after cardiac arrest. Whether these patients would benefit from earlier and more aggressive treatment warrents further research.

The diagnosis of status epilepticus on the electroencephalogram (EEG) in comatose patients after cardiac arrest is controversial[24,28]. It may consist of unequivocal seizures: generalized spike-wave discharges at 3/s or faster or clearly evolving discharges of any type at 4/s or faster, either generalized or focal[29]. However, some experts also consider other rhythmic or periodic patterns, such as generalized or lateralized periodic discharges or rhythmic delta activity, as seizure activity[27,28]. In Chapter 8 we showed by using a computational model, that generalized periodic discharges (GPDs) may result from selective synaptic damage. Therefore, GPDs observed in patients with postanoxic encephalopathy might represent severe ischemic damage instead of

ictal activity. However, it is currently unknown whether this ischemic damage of synapses is potentially reversible and whether treatment with anti-epileptic drugs may promote recovery.

Quantitative EEG analyses

Quantitative EEG analysis can assist in decreasing the time needed for visual interpretation of long EEG recordings and in making the visual analysis more objective[25,30–32]. In Chapter 6 we implemented an automatic system for real-time classification of the EEG in critically ill patients in the ICU. A user interface was developed to present both trend-curves and a diagnostic output in text form. In Chapter 7 we introduced the "Cerebral Recovery Index (CRI)", which is a score ranging from 0 to 1 that can be used for grading of EEGs in patients with postanoxic encephalopathy. Both systems are ready for online use in the ICU. We showed that the use of both systems is feasible. The use of these systems in the clinical setting still has to be evaluated and most likely the user interfaces of both systems have to be adapted. In further development, it is important to keep in mind that the systems are not primarily designed to replace visual analysis[33–35]. Instead, quantitatively EEG analysis should be used to assist in the visual analysis by detecting changes in the EEG and by making a first rough classification of the EEG.

Computational modelling of specific EEG patterns

The EEG measures spontaneous cortical activity, and is a reflection of the synaptic activity of the pyramidal cells in the cortex[9]. More detailed understanding of the generation of specific EEG patterns could increase the insight in the pathological processes of ischemia. In an ideal situation, the EEG gives patient specific information about the location and severity of the brain injury and whether this information is reversible or not. Computational modelling could help to evaluate which brain abnormalities are reflected by each specific EEG pattern. In Chapter 8 we showed that GPDs might be a reflection of selective ischemic damage of glutamatergic synapses.

Future perspectives

The results of the use of EEG for the prediction of neurological outcome are very positive and seem to be robust. The prospective cohort study we performed can be interpreted as a class 1 study according to the definitions for

levels of evidence given by the Oxford Centre for Evidence-based Medicine[36]. In the future, EEG within 24 hours after cardiac arrest should be part of standard post cardiac arrest care. However, before the evidence reaches a level A and clinical guidelines will be changed, an additional independent, preferably multi-centre, study is necessary to confirm our results. Confirming the results in a larger cohort will also tighten the 95% confidence interval.

Another relevant issue concerns the inter-observer-agreement both in offline analysis and in real-time situations. The interobserver agreement of standardized terminology for the description of rhythmic and periodic EEG patterns is known to vary from high or moderate to even slight or fair, with higher values for the main terms and lower values for the more complex, subtle and optional terms[37,38]. Since for the prediction of neurological outcome we look at the background pattern, and the categories we used were defined in a very clear manner, we expect that the interobserver agreement will be high. Furthermore, we also showed that it is possible to quantify the differences in EEG patterns. Still, great care should be taken in the interpretation. The classification of isoelectric and burst suppression EEGs with similar bursts is relatively straightforward. However, there might be discussion in some cases of low voltage EEG patterns that are just above or just below the limit of 20 μV.

The prognostic value of EEG might be increased with further characterization of burst-suppression patterns with non similar bursts. The duration of the suppressions, and the shape and content of the bursts might contain information that is relevant for the neurological prognosis[39,40]. Prediction may be further improved and extended towards other points of time after cardiac arrest by combining neurophysiological, biochemical, and clinical markers.

To answer the question whether treatment of electroencephalographic status epilepticus, including GPDs, is indeed futile, a large randomized control study including early and aggressive treatment is necessary.

In the domain of quantitative EEG analysis, further improvement is also possible. Current systems have to be tested in an ICU environment, since both systems were only evaluated offline. Comments of the treating physicians on their usage have to be studied and the user interface of both systems might have to be improved.

Similar to our study in which we simulated the generation of GPDs, computational modelling can be used for improvement of our understanding of other specific EEG patterns, such as burst suppression patterns with or without similar bursts. Computational modelling is a great tool to test a hypothesis or to generate a new prediction that can be tested experimentally. Therefore computational modelling should be combined with other disciplines such as in vitro or in vivo models or post mortem analysis.

Conclusion

This thesis shows that the EEG contains information that is useful for the prediction of neurological outcome in postanoxic patients treated with mild hypothermia. We show that timing of the EEG is critical and that differences of EEG patterns between patients recovering and not recovering are especially large in the first 24 hours after cardiac arrest. At 24 hours, the combined group of iso-electric, low voltage, and "burst-suppression with identical bursts" was invariably associated with poor outcome. At 12 hours, normal or diffusely slowed EEG patterns were strongly associated with good outcome. Secondly, we implemented two computer algorithms and we showed that quantitative analysis can be used to assist in the interpretation of long-term EEG recordings measured in the ICU. Thirdly, we showed that computational modelling can be used to test a hypothesis on the generation of specific EEG patterns. In our computational model we showed that GPDs can be explained as a reflection of selective ischemic damage of glutamatergic synapses.

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Summary

The electroencephalogram (EEG) contains information that is useful for the prediction of both poor and good neurological outcome in patients with postanoxic encephalopathy after cardiac arrest treated with mild hypothermia. The combined group of iso-electric, low voltage or burst-suppression patterns with identical bursts recorded at 24 hours after cardiac arrest reliably predicts poor neurological outcome with a sensitivity of 48% (CI: 35–60%) and a specificity of 100% (CI: 94–100%) (Chapters 2 and 4). In contrast, the sensitivity for bilateral SSEP absence was only SSEP 24% (CI: 10–44%) (Chapter 2). "Burst-suppression with identical bursts" is a distinct pathological EEG pattern characterized by bursts with a high similarity. Burst-suppression with identical bursts can only be seen after diffuse cerebral ischemia and is inevitably associated with poor neurological outcome (Chapter 3). In addition, normal or diffusely slowed EEG patterns at 12 hours after cardiac arrest are associated with a good neurological outcome with a sensitivity of 57% (CI: 42–71%) and a specificity of 96% (CI: 86–100%) (Chapters 2 and 4).

The increased use of EEG monitoring leads to an increased detection of electrographic seizures and status epilepticus. However, it is currently unknown if and how aggressive patients with these patterns should be treated. In our retrospective study, moderate treatment with anti-epileptic drugs did not improve outcome of patients with electrographic status epilepticus after cardiac arrest (Chapter 5).

Quantitative EEG analysis can assist in decreasing the time needed for visual interpretation of the long EEG recordings and in making the visual analysis more objective. We implemented two computer algorithms that can assist in the interpretation of long EEG recordings. The first system can be used for real-time classification of the EEG in critically ill patients. This system has

an accuracy of 85–88% (Chapter 6). Secondly, we introduced the “Cerebral Recovery Index (CRI)”, which is a score ranging from 0 to 1, that can be used for the grading of EEGs in patients with postanoxic encephalopathy. At 24 hours after cardiac arrest, a CRI < 0.29 was always associated with poor neurological outcome, with a sensitivity of 55% (CI: 32–76%) and a specificity of 100% (CI: 86–100%). At the same time point a CRI > 0.69 predicted good neurological outcome, with a sensitivity of 25% (CI: 10–47%) and a specificity of 100% (CI: 85–100%) in the test set (Chapter 7).

Finally, we showed by using a computational model that generalized periodic discharges, an EEG pattern that can be observed in patients with post-anoxic encephalopathy, can be explained as a reflection of selective ischemic damage of glutamatergic synapses (Chapter 8).

Samenvatting

Het elektro-encefalogram (EEG) bevat kan gebruikt worden voor het voorspellen van zowel goede als slechte neurologische uitkomst in patiënten met postanoxische encefalopathie na een hartstilstand, die behandeld worden met milde therapeutische hypothermie. Een slechte neurologische uitkomst kan 24 uur na de hartstilstand betrouwbaar worden voorspelt op basis van de gecombineerde groep van iso-elektrische, laag gevolteerde en burst-suppressie patronen met identieke bursts, met een sensitiviteit van 48% (95% betrouwbaarheidsinterval: 35–60%) en een specificiteit van 100% (95% betrouwbaarheidsinterval: 94–100%) (Hoofdstukken 2 en 4). Daarentegen, is de sensitiviteit van een bilateraal afwezige SSEP response slechts 24% (95% betrouwbaarheidsinterval: 10–44%) (Hoofdstuk 2). “Burst-suppressie met identieke bursts” is een onderscheidend en pathologisch EEG patroon, dat wordt gekarakteriseerd door bursts met een hoge mate van gelijkenis. Burst-suppressie met identieke bursts kan alleen worden gezien na diffuse cerebrale ischemie en is onvermijdelijk geassocieerd met slechte neurologische uitkomst (Hoofdstuk 3). Daarnaast zijn normale of diffuus vertraagde EEG patronen, gemeten 12 uur na de hartstilstand sterk geaccocieerd met een goede neurologische uitkomst, met een sensitiviteit van 57% (95% betrouwbaarheidsinterval: 42–71%) en een specificiteit van 96% (95% betrouwbaarheidsinterval: 86–100%) (Hoofdstukken 2 and 4).

Het toegenomen gebruik van EEG monitoring leidt tot een toename in de detectie van elektrografische insulten en status-epilepticus. Echter, op dit moment is het nog onduidelijk of en hoe agressief patiënten met deze patronen behandeld moeten worden. In onze retrospectieve studie liet een gematigde behandeling met anti-epileptica geen verbetering zien in de uitkomst van patiënten met een elektrografische status-epilepticus na een hartstilstand (Hoofdstuk 5).

Kwantitatieve EEG analyse kan helpen om de tijd die nodig is voor visuele interpretatie van langdurige EEG registraties te reduceren en om de visuele analyse objectiever te maken. We hebben twee computer algoritmes geïmplementeerd die kunnen bijdragen aan de interpretatie van langdurige EEG registraties. Het eerste systeem kan gebruikt worden voor real-time classificatie van het EEG in patiënten op de intensive care afdeling. Dit systeem heeft een nauwkeurigheid van 85–88% (Hoofdstuk 6). Daarnaast hebben we de "Cerebral Recovery Index (CRI)" geintroduceerd, dit is een score van 0 tot 1, die gebruikt kan worden voor het graderen van EEGs in patiënten met postanoxische encefalopathie. Op het tijdstip 24 uur na de hartstilstand, was een CRI < 0.29 altijd geassocieerd met een slechte neurologische uitkomst, met een sensitiviteit van 55% (CI: 32–76%) en een specificiteit van 100% (95% betrouwbaarheidsinterval: 86–100%). Op hetzelfde tijdstip, voorspelde een CRI > 0.69 goede neurologische uitkomst met een sensitiviteit van 25% (95% betrouwbaarheidsinterval: 10–47%) en een specificiteit van 100% (95% betrouwbaarheidsinterval: 85–100%) in de test set (Hoofdstuk 7).

Tot slot, hebben we met behulp van een computer model aangetoond dat gegeneraliseerde periodieke ontladingen, een EEG patroon dat kan worden gezien in patiënten met postanoxische encefalopathie, verklaard kunnen worden door selectieve ischemische schade van glutamaterge synapsen (Hoofdstuk 8).

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Enschede, januari 2014,

Marleen Tjepkema-Cloostermans

Biography

Marleen Tjepkema-Cloostermans was born on August 6th 1985, in Enschede, The Netherlands. She attended the Jacobus College in Enschede (later named Bonhoeffer College), from which she graduated in 2003. She then started the study Technical Medicine at the University of Twente, and 3 years later with the master track Medical Signaling. As part of this curriculum she did four short internships at the departments of pulmonary medicine, clinical neurophysiology and cardiology in the Medisch Spectrum Twente in Enschede, and the department of intensive care medicine in the UMC St Radboud Hospital in Nijmegen. In June 2009 she obtained her master degree under supervision of prof. dr. ir. M.J.A.M. van Putten with thesis title “Monitoring the brain in the ICU”.

In September 2009 she started her PhD Research at the department of Clinical Neurophysiology of the Univeristy of Twente, of which the content is described in this thesis.

List of publications

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