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DISSERTATION

Cortical somatosensory evoked potential amplitudes and severity of hypoxic-ischemic encephalopathy after cardiac arrest

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Abstract

Introduction: Bilaterally absent median nerve cortical somatosensory evoked potentials (SSEPs) are a reliable prognostic parameter to early predict poor outcome in comatose cardiac arrest (CA) patients if sufficient recording criteria are fulfilled. However, the prognostic significance of cortical SSEP amplitudes and tolerable cortical noise level remain uncertain. Methods: We investigated the prognostic value of cortical SSEP amplitudes to predict poor and good outcome after CA. First, we prospectively determined cortical broadband SSEP amplitudes and clinical outcome upon intensive care unit discharge. Clinical outcome was assessed according to cerebral performance category (CPC) scale and dichotomized in good (CPC 1 – 3) and poor outcome (CPC 4 – 5). Second, we retrospectively studied amplitudes of high-frequency (600 Hz) SSEP components. Third, we retrospectively investigated cortical broadband SSEP amplitudes and severity of hypoxic-ischemic encephalopathy (HIE) in CPC 5 patients histopathologically evaluated by postmortem brain autopsies and dichotomized into no/mild and severe HIE. Results: Of 293 CA patients, 0.62 µV was the lowest cortical broadband SSEP amplitude of 156 good outcome patients whereas all 78 patients with lower amplitudes had a poor outcome. Prognostic parameters, case reviews and amplitude distribution of CPC 4 patients strongly indicated absence of severe HIE in patients with cortical broadband SSEP amplitudes above 2.5 µV. We detected early and late high-frequency (600 Hz) SSEP components in 146 and 95 of 302 included patients. High amplitudes of late high-frequency (600 Hz) SSEP components were mainly found in patients with high cortical broadband SSEP amplitudes. We assessed severe HIE unlikely in patients with late high-frequency (600 Hz) SSEP component amplitudes above 70 nV. Of 187 deceased CA patients with brain autopsy, the lowest cortical broadband SSEP amplitude in 24 patients with no/mild histopathological HIE was 0.5 µV. We found severe histopathological HIE in all 26 patients with cortical broadband SSEP amplitudes below 0.5 µV of whom 21 patients had bilaterally absent cortical SSEPs. Conversely, considering confounders the highest cortical broadband SSEP amplitude in patients with severe histopathological HIE was 2.7 µV. Conclusion: Cortical noise levels should not exceed 0.5 µV to avoid falsely classifying cortical SSEPs as bilaterally absent in good outcome patients. Bilaterally absent cortical SSEPs and cortical broadband SSEPs below 0.5 µV are reliable prognostic parameters for severe HIE evaluated by clinical outcome and brain autopsy. Cortical broadband SSEP amplitudes above 2.7 µV and late high-frequency (600 Hz) SSEP component amplitudes above 70 nV suggest absence of severe HIE.

Abstrakt

Einleitung: Bilateral fehlende kortikale somatosensorisch evozierte Potentiale (SSEPs) nach Nervus medianus Stimulation sind unter Beachtung ausreichender Aufnahmestandards ein zuverlässiger Prognoseparameter um frühzeitig ein schlechtes Outcome bei komatösen Patienten nach Herzstillstand vorherzusagen. Allerdings ist die prognostische Bedeutung von kortikalen SSEP Amplituden und tolerierbare kortikale Rauschlevel ungewiss. Methodik: Wir untersuchten die prognostische Wertigkeit von kortikalen SSEP Amplituden um nach Herzstillstand ein schlechtes und gutes Outcome vorherzusagen. Erstens untersuchten wir prospektiv kortikale Breitband-SSEP Amplituden und das klinische Outcome bei Entlassung von der Intensivstation. Das klinische Outcome wurde mit der Cerebral Performance Category (CPC) Skala erfasst und in gutes (CPC 1 – 3) und schlechtes Outcome (CPC 4 – 5) dichotomisiert. Zweitens studierten wir retrospektiv die Amplituden von hochfrequenten (600 Hz) SSEP Komponenten. Drittens evaluierten wir retrospektiv kortikale Breitband-SSEP Amplituden und den Schweregrad der hypoxisch-ischämischen Enzephalopathie (HIE) bei CPC 5 Patienten histopathologisch mit postmortem Hirnautopsien und dichotomisierten in keine/milde und schwere HIE. Ergebnisse: Von 293 Herzstillstandpatienten war 0.62 μV die niedrigste kortikale Breitband-SSEP Amplitude unter 156 Patienten mit gutem Outcome wohingegen alle 78 Patienten mit niedrigeren Amplituden ein schlechtes Outcome hatten. Prognostische Parameter, Fallübersichten und die Amplitudenverteilung von CPC 4 Patienten deuteten stark auf die Abwesenheit schwerer HIE bei Patienten mit kortikalen Breitband-SSEP Amplituden über 2.5 μV hin. Frühe und späte hochfrequente (600 Hz) SSEP Komponenten wurden bei 146 und 95 von 302 inkludierten Patienten detektiert. Hohe Amplituden von späten hochfrequenten (600 Hz) SSEP Komponenten wurden vor allem bei Patienten mit hohen kortikalen Breitband-SSEP Amplituden gefunden. Eine schwere HIE erschien bei Patienten mit späten hochfrequenten (600 Hz) SSEP Komponentamplituden über 70 nV unwahrscheinlich. Von 187 verstorbenen Herzstillstandpatienten mit Hirnautopsie war 0.5 μV die niedrigste kortikale Breitband-SSEP Amplitude bei 24 Patienten mit keiner/milder histopathologischer HIE. Alle 26 Patienten mit kortikalen Breitband-SSEP Amplituden unter 0.5 μV zeigten eine schwere histopathologische HIE von denen 21 bilateral fehlende kortikale SSEPs hatten. Umgekehrt war nach Ausschluss von Störfaktoren 2.7 μV die höchste kortikale Breitband-SSEP Amplitude von Patienten mit schwerer histopathologischer HIE. Schlussfolgerung: Kortikale Rauschlevel sollten 0.5 μV nicht überschreiten um fälschlicherweise SSEPs als bilateral kortikal fehlend zu klassifizieren bei Patienten mit gutem klinischem Outcome. Bilateral fehlende kortikale SSEPs und kortikale Breitband-SSEP Amplituden unter 0.5 μV sind zuverlässige Prognoseparameter für schwere HIE

anhand des klinischen Outcomes und Hirnautopsien. Kortikale Breitband-SSEP Amplituden über 2.7 μV und späte hochfrequente (600 Hz) SSEP Komponentamplituden über 70 nV sprechen für die Abwesenheit von schwerer HIE.

1. Introduction

Cardiac arrest (CA) is a devastating disease with a global incidence of out-of-hospital cardiac arrest of 55/100.000 person-years (Berdowski et al., 2010; Rossetti et al., 2016; Bjørshol and Søreide, 2017). Over previous decades, the rate of CA survivors has significantly increased due to improvements in the chain of survival including higher bystander resuscitation rates (Lindner et al., 2011; Bjørshol and Søreide, 2017), improved prehospital advanced life support and postresuscitation care (Callaway et al., 2015; Nolan et al., 2015; Rossetti et al., 2016; Bjørshol and Søreide, 2017), acute availability to coronary angiography (Patterson et al., 2018) and the introduction of targeted temperature management (TTM) (Kirkegaard et al., 2019). In a large international, multicenter, randomized trial on TTM (Nielsen et al., 2013), approximately half of CA patients with return of spontaneous circulation (ROSC) survived long-term.

If the survival in the early phase after successful resuscitation is achieved (Dragancea et al., 2013; Nobile et al., 2016), the severity of hypoxic-ischemic encephalopathy (HIE) critically determines the neurological outcome and hence overall clinical outcome (Greer et al., 2014; Rossetti et al., 2016; Elmer and Callaway, 2017). Several prognostic parameters have been established to predict poor outcome in comatose CA patients within the first days after resuscitation and guide decisions on withdrawal of life-sustaining therapy (WLST) in patients with severe HIE (Greer et al., 2014; Sandroni et al., 2014; Callaway et al., 2015; Rossetti et al., 2016). Reflecting different pathophysiological aspects of the HIE, clinical examination (Wijdicks et al., 2006; Greer et al., 2014), serum biomarkers like neuron-specific enolase (NSE) (Stammet et al., 2015; Streitberger et al., 2017), neurofilament light chain (Moseby-Knappe et al., 2019) and tau protein (Mattsson et al., 2017), gray-white-matter ratio of brain computed tomography (CT) (Metter et al., 2011; Scheel et al., 2013; Streitberger et al., 2019), electroencephalography (EEG) (Rossetti et al., 2009; Westhall et al., 2016; Ruijter et al., 2019) and median nerve somatosensory evoked potentials (SSEPs) (Zandbergen et al., 2006b; Leithner et al., 2010; Bouwes et al., 2012; Horn and Tjepkema-Cloostermans, 2017; Maciel et al., 2017) are routinely used in a multimodal neuroprognostication algorithm (Leithner et al., 2012; Sandroni et al., 2014; Callaway et al., 2015).

The bilateral absence of cortical SSEPs after electrical median nerve stimulation is the most reliable prognostic parameter that early predicts poor outcome in comatose CA patients as highlighted in the current international guidelines of the European Resuscitation Council (Sandroni et al., 2014) and the American Heart Association (Callaway et al., 2015). However, rare exceptions of comatose CA survivors regaining consciousness despite bilateral absence of cortical SSEPs have been reported in larger studies (Leithner et al., 2010; Bouwes et al., 2012; Dragancea

et al., 2015) and detailed case reports (Leithner et al., 2010; Bender et al., 2012; Arch et al., 2014; Codeluppi et al., 2014; Pfeiffer et al., 2014) and were discussed in the recent meta-analysis (Amorim et al., 2018). Of course, low false positive rates for bilaterally absent SSEPs in the comatose CA patients are absolutely required considering the dramatic therapeutic consequences frequently leading to WLST according to current international multimodal neuroprognostication algorithms (Sandroni et al., 2014; Callaway et al., 2015). Most importantly, there have often been too high noise levels leading to artefacts during SSEP recordings (Bouwes et al., 2012; Codeluppi et al., 2014; Dragancea et al., 2015; Karunasekara et al., 2016) and incomplete clinical data in these patients (Amorim et al., 2018). Unfortunately, reliable guidelines on tolerable cortical noise levels for SSEP recordings are hitherto lacking (Cruccu et al., 2008). Furthermore, differences in recording technique and analysis of cortical SSEPs (Sherman et al., 2000; Bauer et al., 2003) and an only moderate inter-observer reliability (Zandbergen et al., 2006a; Pfeifer et al., 2013) impedes the classification of cortical SSEPs as present.

In the present thesis, three studies are summarized that investigated the relationship between cortical SSEP amplitudes and the severity of HIE evaluated by clinical and histopathological outcome. The main aim was to establish cortical SSEP amplitudes as an early prognostic parameter to predict poor and good outcome after CA and to thereby define a tolerable cortical noise level to avoid false classification of cortical SSEPs as bilaterally absent.

2. Methods

2.1 Patients, clinical outcome and withdrawal of life-sustaining therapy

The three studies of this thesis were approved by local ethics committees. In study 1 and study 2, we consecutively prospectively enrolled CA patients admitted to the Charité Universitätsmedizin Berlin at Campus Virchow-Klinikum between May 2009 and April 2014 (study 1) and May 2009 and August 2014 (study 2). We included comatose patients routinely investigated with median nerve SSEPs one to four days after CA (Endisch et al., 2015, 2016). Following current international guidelines on intensive care treatment of CA patients (Sandroni et al., 2014; Callaway et al., 2015), TTM was induced within the first four hours, maintained at 33 °C for 24 hours and followed by a re-warming period (0.25 °C per hour) (Nielsen et al., 2013). We routinely used fentanyl and midazolam/inhalational anesthetics for sedation and analgesia and prevented shivering by magnesium and warming of extremities (Endisch et al., 2015, 2016)

To assess the clinical outcome, we determined the Cerebral Performance Category (CPC) score upon intensive care unit (ICU) discharge (Booth et al., 2004). CPC 1 comprises conscious patients with no or only minor cerebral disabilities, CPC 2 consciousness and moderate cerebral disabilities, CPC 3 consciousness and severe cerebral disabilities including minimally conscious states (Demertzi et al., 2015), CPC 4 coma and patients surviving with an unresponsive wakefulness syndrome and CPC 5 death (Booth et al., 2004).

Importantly, neuroprognostication studies are potentially susceptible to a self-fulfilling prophecy if an investigated prognostic parameter is used in the decision process leading to WLST (Greer et al., 2014). In our institution, we hence adhered to a multimodal neuroprognostication algorithm including NSE serum concentration above 97 µg/l after excluding possible confounders for NSE elevations and the bilateral absence of pupillary reflexes and cortical SSEPs on day three after CA (Leithner et al., 2012). Unless all three criteria were fulfilled and except from cases with preexisting malignant disease or otherwise stated patient directives, therapy withdrawal was only discussed in comatose CA patients with repeated and additional prognostic diagnostics who were at least treated seven days (Leithner et al., 2012). We highlight that our multimodal neuroprognostication algorithm included bilaterally absent cortical SSEPs on day three after CA but not the determination of cortical SSEP amplitudes prior to the presented studies (Leithner et al., 2012; Storm et al., 2019).

2.2 Median nerve SSEP recordings

We recorded median nerve SSEPs with a Nihon Kohden Neuropack M1 MEB-9200 G and attached AgCl-electrodes according to the international 10 – 20 system of electrode placement (Seeck et al., 2017). SSEP recordings included at least two peripheral (NErb, supraclavicular fossa), cervical (N13a, level C7) and cortical channels (CP3 and CP4, CP ipsi- and contralateral). Standard recording requirements were: skin-electrode impedance below 5000 Ω, ground electrode placed proximal to stimulation, reference electrode placed midfrontal (Fz), 200 µs monophasic square-wave stimulation pulses, supramaximal motor threshold stimulation intensity to elicit visible thumb twitching, 2.7 Hz stimulation frequency, 5 – 1500 Hz band pass width, 20480 Hz sample rate, recording duration – 1 ms to 49 ms post stimulus (Endisch et al., 2015, 2016). We refer to the method section of our original studies for more technical details (Endisch et al., 2015, 2016). To reduce muscle artefacts during SSEP recordings, short-lasting muscle relaxants and sedatives were administered if necessary. In artefact-prone or low-amplitude cortical SSEPs, we obtained a third SSEP recording. We digitalized and anonymized SSEP recordings for further analysis using custom-written MATLAB (www.mathworks.com) scripts.

2.3 Determination of cortical broadband SSEP amplitudes

We excluded SSEP recordings without at least two peripheral, cervical and cortical recordings, bilaterally reproducible N13a potentials (Cruccu et al., 2008) or cortical noise levels above 0.25 μV (defined as peak-to-peak noise level within the 5 – 10 ms interval) in one cortical recording unless cortical broadband SSEP amplitudes were above 1 μV (Endisch et al., 2015). The amplitudes of reproducible baseline – N1 (baseline – N20) and N1 – P1 (N20 – P25) potentials were determined if the N13a – N20 latency was longer than 4.5 ms. We rarely determined the amplitude of extreme values of an atypical but reproducible cortical potential. The cortical broadband SSEP amplitude was defined as maximum amplitude of all cortical potentials. To classify SSEP recordings as bilaterally absent, noise levels had to be below 0.25 μV in cortical recordings with no reproducible cortical SSEPs (Endisch et al., 2015).

2.4 Analysis of high-frequency (600 Hz) SSEP components

We interpolated stimulation artefacts employing monotone cubic Hermite spline interpolation (Waterstraat et al., 2015; Endisch et al., 2016) and filtered cortical recordings with a finite impulse response filter (450 – 750 Hz band pass width) (Jones and Barth, 2002; Delorme and Makeig, 2004; Ozaki and Hashimoto, 2011). The N1 – peak distinguished the early and late component of isolated high-frequency oscillation (HFO) bursts around 600 Hz (Ikeda et al., 2002; Ozaki and Hashimoto, 2011). If two peaks exceeded baseline plus threefold standard deviation of cortical noise level (defined as peak-to-peak noise level within the 35 – 45 ms interval) (Gobbelé et al., 2004, 2008b, 2008a; Endisch et al., 2016) the low-amplitude high-frequency (600 Hz) SSEP components were classified as present and maximum peak-to-peak amplitudes of early and late HFO bursts determined.

2.5 Investigating potential confounders of SSEP recordings

Prior to SSEP recordings, we measured the body temperature and cumulative twelve-hour dosages of sedatives and analgesics and investigated the relationship between body temperature, sedation and cortical SSEP amplitudes in study 1 (Endisch et al., 2015) and study 2 (Endisch et al., 2016). Patients without sedatives and analgesics in the last twelve hours were classified as non-sedated. The remaining patients were considered deeply (the third of pateints with highest dosages of sedatives) and mildly (the third of patients with lowest dosages of sedatives) sedated. We also assessed the clinical presentation of posthypoxic myoclonus during the ICU stay in study 2 (Endisch et al., 2016).

2.6 Extracerebral causes of death

Extracerebral complications like sepsis, multi-organ-failure, cardiopulmonary failure or a second CA frequently occur in patients after initially successful resuscitation (Dragancea et al., 2013; Nobile et al., 2016). These complications may lead to secondary brain injury and/or death in patients who survived the initial CA without severe HIE. Neuroprognostication studies aiming to investigate prognostic parameters for good outcome may be profoundly confounded by this fact (Greer et al., 2014; Rossetti et al., 2016).

We hence reviewed deceased patients (i.e. CPC 5 patients) with amplitudes of cortical broadband SSEPs and late high-frequency SSEP components larger than the lowest amplitude recorded in CPC 4 patients (Endisch et al., 2015, 2016). This approach was chosen as patients with a CPC 4 outcome upon ICU discharge had the clinical proof of severe HIE. Case reviews included whether patients temporarily regained consciousness (i.e. awake and communicating) after CA, autopsy reports, other prognostic parameters, preexisting diseases, durations of ROSC and ICU stays, causes of death and decisions leading to therapy withdrawal (Endisch et al., 2015, 2016).

2.7 Histopathological severity of HIE in brain autopsy

To extend our analysis on SSEPs of CPC 5 patients, we validated in a third study the amplitude thresholds of cortical broadband SSEPs in CPC 5 patients with post-CA SSEP recordings who underwent postmortem brain autopsies (Endisch et al., 2020). We retrospectively identified deceased CA patients with post-CA SSEP recordings and postmortem brain autopsies at the Charité Universitätsmedizin Berlin (Campus Virchow-Klinikum, Campus Charité Mitte and Campus Benjamin Franklin), Skåne University Hospital Lund, Sweden, and Århus University Hospital, Denmark, between 2003 and 2015. SSEP recordings were blinded from other neuroprognostication and clinical data retrospectively reevaluated and cortical broadband SSEP amplitudes determined according to methods of study 1 (Endisch et al., 2015) and study 2 (Endisch et al., 2016).

We microscopically analyzed available hematoxylin-eosin staining of formaldehyde-fixed brain sections including oxygen-sensitive regions (cerebral neocortex, hippocampus and cerebellum) and brain stem (mesencephalon, pons and medulla oblongata). The severity of HIE was quantified using the selective eosinophilic neuronal death (SEND) classification (Horn and Schlote, 1992; Högler et al., 2010; Björklund et al., 2014; Putten et al., 2018). The SEND classification employs the histopathological finding that neuronal death following CA and successful resuscitation with cerebral reperfusion shows as red and pycnotic neurons without cytoplasmic-nuclear borders and spared neuropil

(Horn and Schlote, 1992; Högler et al., 2010; Björklund et al., 2014; Putten et al., 2018). Neuronal death was classified as none (SEND 0), below 30 % (SEND 1), 30 – 60 % (SEND 2), 60 – 90 % (SEND 3) or more than 90 % (SEND 4) as previously suggested (Björklund et al., 2014). Based on findings whether patients temporarily regained consciousness, we dichotomized patients into "no/mild HIE" if neuronal death was less than 30 % (SEND 0 – 1) in the cerebral cortex and brain stem and "severe HIE" if neuronal death exceeded 30 % in any brain region.

We then investigated the relationship between amplitudes of cortical broadband SSEPs and patients histopathologically classified as "no/mild HIE" or "severe HIE".

3. Results

3.1 Cortical broadband SSEP amplitudes and clinical outcome

In study 1 (Endisch et al., 2015), we prospectively investigated the relationship between clinical outcome and cortical broadband SSEP amplitudes of 293 included CA survivors after excluding 25 (7.9 %) patients due to insufficient technical requirements. The cortical broadband SSEP amplitude distributions showed a large overlap between CPC outcome groups except from CPC 4 patients. Cortical broadband SSEP amplitudes were not influenced by recording time of SSEPs after CA, depth of sedation or body temperature.

Bilaterally absent SSEPs were found in 41 patients all of whom were discharged dead or with CPCP 4 yielding a sensitivity for prediction of poor outcome of 30 %. The lower cortical broadband SSEP amplitude threshold of 156 patients surviving with CPC 1 – 3 was 0.62 µV. 78 of 137 patients discharged with CPC 4 – 5 had a broadband SSEP amplitude below 0.62 µV. A cortical broadband SSEP amplitude below 0.62 µV thus predicted poor outcome with a sensitivity of 57 %.

We did not find cortical broadband SSEP amplitudes above 2.5 µV in any of the 27 CPC 4 patients. As survival with CPC 4 provides clinical evidence for severe HIE, we assessed 24 CPC 5 patients with cortical broadband SSEP amplitudes above 2.5 µV. Brain autopsy results and the temporary regain of consciousness after SSEP recordings excluded severe HIE in ten of these patients. In the remaining patients, the combined information on available prognostic parameters, preexisting diseases, course of resuscitation, duration of ICU stay and death causes strongly suggested the absence of HIE incompatible with regaining consciousness. Specifically, we did not find highly-malignant EEG patterns according to Westhall et al. (Westhall et al., 2016) except from two cases and thirteen brain

CTs without evidence of severe HIE. Moreover, available median NSE values obtained three days after CA were 24 µg/l (inter-quartile range 17 – 36) in these CPC 5 patients compared to 74 µg/l (inter-quartile range 39 – 164) in CPC 4 and 19 µg/l (inter-quartile range 14 – 26) in CPC 1 – 2 patients. Following results in this thesis are presented as median value with inter-quartile range in brackets unless noted differently. The prediction of good outcome employing the cortical broadband SSEP amplitude threshold of 2.5 µV yielded a sensitivity of 65 %.

3.2 High-frequency (600 Hz) SSEP component amplitudes and clinical outcome

In study 2 (Endisch et al., 2016), we retrospectively analyzed high-frequency (600 Hz) SSEP components of 302 included CA patients, 152 (50.3 %) surviving with CPC 1 – 3 and 150 (49.7 %) patients with CPC 4 – 5. Cortical peak-to-peak noise levels did not exceed 100 nV and 50 nV in 294 (97 %) and 253 (84 %) patients, respectively. We found 146 (48 %) patients with significant early and 95 (32 %) patients with late high-frequency SSEP components. Late high-frequency SSEP components were detected in 44.1 % (67 of 152) of CPC 1 – 3 patients compared to 18.7 % (28 of 150) of CPC 4 – 5 patients. High-frequency SSEP component amplitudes were not influenced by body temperature, depth of sedation or posthypoxic myclonus.

Late high-frequency SSEP components were only present in four of 27 CPC 4 patients. Except from one patient with a significant long-term improvement in outcome, CPC 4 patients did not exceed late high-frequency SSEP component amplitudes of 70 nV. In eight of seventeen CPC 5 patients with late high-frequency SSEP component amplitudes above 70 nV, severe HIE was assessed absent as patients temporarily regained consciousness during the ICU stay or brain autopsy showed no histopathological severe HIE. In the remaining patients, the available neuroprognostication and the ICU course suggest absence of severe HIE incompatible with good outcome. Combining a late high-frequency SSEP component amplitude threshold of 70 nV with a cortical broadband SSEP amplitude threshold of 2.5 µV yielded a sensitivity of 69 % for the prediction of good outcome.

3.3 Cortical broadband SSEP amplitudes and histopathological severity of HIE

In study 3 (Endisch et al., 2020), we retrospectively included 187 deceased CA patients with initially successful resuscitation and neuroprognostication who underwent postmortem brain autopsies. SSEP recordings were performed in 58 patients of whom 34 patients had histopathologically severe HIE and 24 patients no/mild HIE. The median cortical broadband SSEP amplitude in the 34 patients with severe HIE was 0 µV (i.e. absent, 0 – 0.4) compared to 2.5

μV (1.7 – 4.0) in the 24 no/mild HIE patients. Lower cortical broadband SSEP amplitudes up to bilaterally absent cortical SSEPs were associated with more pronounced histopathologically quantified neuronal death in the analyzed brain regions, especially in the cerebral cortex. The lowest cortical broadband SSEP amplitude in patients with no/mild HIE was 0.5 μV. Conversely, all 21 patients with bilaterally absent cortical SSEPs and 5 patients with cortical broadband SSEP amplitudes below 0.5 μV showed severe HIE.

In two severe HIE patients, we found exceptionally high cortical broadband SSEP amplitudes of 3.5 μV and 2.7 μV. The first patient temporarily regained consciousness after the SSEP recording but suffered from a second CA probably leading to additional brain injury and severe HIE in the postmortem brain autopsy. For the latter patient, we could not identify plausible confounders. Hence, after considering confounders 2.7 μV was the upper threshold of cortical broadband SSEP amplitudes in CA patients with severe histopathological HIE.

4. Discussion

The main findings of the present thesis are: (1) Bilaterally absent cortical SSEPs in comatose CA patients are a reliable prognostic parameter to predict poor outcome and are associated with severe histopathological HIE. (2) Severe histopathological HIE in all patients with bilaterally absent cortical SSEPs argue against a self-fulfilling prophecy in current practice to use SSEPs in a multimodal neuroprognostication algorithm. (3) Low-amplitude cortical broadband SSEP amplitudes below 0.5 μV are also predictive of severe HIE evaluated by clinical outcome and brain autopsy. (4) Cortical noise levels should not exceed 0.5 μV to avoid false classification of cortical SSEPs as bilaterally absent. (5) Cortical broadband SSEP amplitudes above 2.7 μV suggest absence of severe HIE in clinical outcome and brain autopsy. (6) Non-invasive recording of high-frequency (600 Hz) SSEP components is feasible in an ICU setting and late high-frequency SSEP component amplitudes above 70 nV argue for absence of severe HIE.

4.1 Standardized protocol of SSEP recordings

To study cortical SSEP amplitudes as a prognostic parameter in CA patients, we first established a standardized SSEP recording and interpretation protocol with focus on minimizing cortical noise levels during SSEP recordings (Endisch et al., 2015, 2016). This approach was important as insufficient cortical noise levels impeded the classification of cortical SSEPs as present and contributed to false interpretations and a surprisingly moderate inter-observer reliability

in previous studies and case reports (Zandbergen et al., 2006a; Bouwes et al., 2012; Pfeifer et al., 2013; Codeluppi et al., 2014; Dragancea et al., 2015; Karunasekara et al., 2016).

Sherman et al. (Sherman et al., 2000) and Bauer et al. (Bauer et al., 2003) previously only considered cortical broadband SSEPs with amplitudes more than 0.3 μV and 0.1 μV, respectively, as present and Zandbergen et al. (Zandbergen et al., 2006a) surprisingly concluded that bilaterally absent cortical SSEPs still reliably predict poor outcome despite the finding of moderate inter-observer reliability. The lack of accurate reporting of technical details of SSEP recording and interpretation in some previous studies (Bouwes et al., 2012; Codeluppi et al., 2014; Karunasekara et al., 2016; Amorim et al., 2018) surprises considering the dramatic therapeutic consequences in comatose CA patients with bilaterally absent cortical SSEPs (Sandroni et al., 2014; Callaway et al., 2015). Hence, we thoroughly described our technical details of SSEP recordings and thereby also facilitated future inter-study comparison.

To maximally reduce muscle artefacts, we administered short-acting relaxants and sedatives if necessary, and bilaterally recorded at least two averaged sets of 500 single recordings as recommended by the International Federation of Clinical Neurophysiology (IFCN) (Cruccu et al., 2008). Due to previous results of decreased inter-observer reliability in patients with higher cortical noise levels (Zandbergen et al., 2006a) SSEP recordings with cortical noise levels larger than 0.25 μV were excluded unless cortical broadband SSEP amplitudes exceeded 1 μV. Only maximum peak-to-peak amplitudes of reproducible cortical broadband SSEPs with N13a – N20 latencies larger than 4.5 ms were considered to avoid falsely determining amplitudes of far-field artefacts (Cruccu et al., 2008). Following these strict recording and inclusion criteria, we only excluded 7.9 % of 318 patients with SSEP recordings in study 1 (Endisch et al., 2015) compared to up to 40.2 % excluded patients in another study (Cruse et al., 2014). In accordance to the IFCN recommendations (Cruccu et al., 2008) and previous studies (Zandbergen et al., 2006b, 2006a; Leithner et al., 2010; Pfeifer et al., 2013) we recorded cortical SSEPs using the scalp electrode placement at CP3/CP4 referenced to Fz. This recording detail is important as the absolute values of cortical broadband SSEP amplitudes vary from the relative proximity of scalp electrodes (Allison et al., 1991). Hence, only experienced technicians strictly following the international 10 – 20 system (Seeck et al., 2017) of electrode placement should perform SSEP recordings. We recorded with a 2.7 Hz stimulation frequency and supramaximal stimulation intensities above motor threshold to provide a maximal potential recruitment (Cruccu et al., 2008; Gobbelé et al., 2008a). Different stimulation settings may lead to different SSEP amplitudes and need to be considered in future studies. In our institution, we recorded SSEPs with a 5 – 1500 Hz band pass filter that differed from previous studies (Sherman et al., 2000; Zandbergen et al., 2006a, 2006b) and the IFCN recommendations (Cruccu et al., 2008). Considering the SSEP

frequency spectrum (Ozaki and Hashimoto, 2011), the typically used lower band pass edge thresholds may not profoundly influence the peak waveform of the N1 – P1 potential but may alter the low-frequency SSEP baseline curve (Eisen et al., 1984). Importantly, in only few patients, baseline – N1 potentials were the maximum cortical broadband SSEP potentials (Endisch et al., 2015). Strict adherence to a standardized band pass filter setting and detailed technical SSEP reporting would be desirable to ensure inter-study comparison on SSEP amplitudes and have been implemented in current studies (Oh et al., 2019; Barbella et al., 2020; Glimmerveen et al., 2020). We found no influence of body temperature, depth of sedation, posthypoxic myoclonus and recording time after CA on cortical SSEP amplitudes (Endisch et al., 2015, 2016). These findings are important in clinical practice and corroborate the known finding that short-latency cortical SSEPs are more robust against sedatives than EEG (Langeron et al., 1997; Banoub et al., 2003; Horn and Tjepkema-Cloostermans, 2017). SSEP recordings and amplitudes may hence be used as an early prognostic parameter in still sedated CA patients. However, until further studies have investigated possible confounding factors on cortical SSEPs and amplitudes, SSEPs should be recorded after re-warming from TTM three days after CA as recommended in the international guidelines (Sandroni et al., 2014; Callaway et al., 2015).

4.2 Bilaterally absent and low-amplitude cortical broadband SSEPs below 0.5 µV predict poor outcome

Bilaterally absent cortical SSEPs were a reliable prognostic parameter of poor outcome in previous neuroprognostication studies (Greer et al., 2014; Rossetti et al., 2016). In most recent studies (Choi et al., 2017; Kim et al., 2018; Carrai et al., 2019; Oh et al., 2019, 2020; Scarpino et al., 2019; Barbella et al., 2020; Glimmerveen et al., 2020; Nobile et al., 2020), bilateral absence of cortical SSEPs have been exclusively associated with poor outcome some of which did not perform therapy withdrawal due to legal restrictions. In line with these findings, in our studies (Endisch et al., 2015, 2016), none of the CA patients with bilaterally absent SSEPs was discharged with a good outcome and all 21 brain autopsy patients with bilateral absence of cortical SSEPs showed severe histopathological HIE (Endisch et al., 2020). Hence, severe HIE incompatible with the long-term regain of consciousness is highly likely in patients if the somatosensory cortex is unable to generate cortical SSEPs after initial survival of CA (Putten, 2012). Importantly, adherence to a standardized SSEP recording and interpretation protocol and reduction of cortical noise levels is important to ensure inter-observer reliability and to classify cortical SSEPs as bilaterally absent (Zandbergen et al., 2006a; Pfeifer et al., 2013).

Pathophysiologically, the prognostic principle of bilaterally absent cortical SSEP is based on a pars pro toto approach of global hypoxic-ischemic brain injury following CA in which the neuronal hypoxic-ischemic damage of a specific

cortical region indicates the severity of HIE of the entire cerebral cortex (Putten, 2012; Elmer and Callaway, 2017). The severity of HIE is thereby mainly determined by the initial cerebral no-flow and low-flow period during CA resuscitation (Dankiewicz et al., 2016; Reynolds et al., 2016) and secondary brain injury causing histopathologically selective neuronal death and/or depending on CA duration infarction of the oxygen-sensitive cerebral cortex (Horn and Schlote, 1992; Högler et al., 2010; Björklund et al., 2014; Putten et al., 2018).

However, it is important to consider exceptionally rare cases of CA patients surviving with good outcome despite bilaterally absent cortical SSEPs in SSEP recordings with sufficient quality and documentation (Leithner et al., 2010; Bender et al., 2012; Arch et al., 2014; Pfeiffer et al., 2014). Diffusion weighted imaging revealed brain injury mainly restricted to the somatosensory cortex in one case (Pfeiffer et al., 2014) indicating the possibility of heterogenous cortical damage. Hence, we recommend to use the prognostic parameter of bilaterally absent cortical SSEPs always in a multimodal neuroprognostication algorithm with consideration of possible confounders (Sandroni et al., 2014; Callaway et al., 2015).

The lowest cortical broadband SSEP amplitude in CA patients with good outcome and histopathological absence of severe HIE in brain autopsies, respectively, was 0.5 µV (Endisch et al., 2015, 2016, 2020). Hence, we concluded that SSEP recordings should at least aim for cortical noise levels below 0.5 µV to avoid noise levels potentially exceeding low-amplitude cortical SSEPs of patients without severe HIE. This lower amplitude threshold for a CA patient with good outcome was corroborated in recent SSEP studies ranging from 0.40 – 0.65 µV with slight methodological differences in mind (Choi et al., 2017; Carrai et al., 2019; Glimmerveen et al., 2019; Oh et al., 2019; Barbella et al., 2020).

Surprisingly, we found a relationship between cortical broadband SSEP amplitudes and clinical outcome (Endisch et al., 2015). All patients with cortical broadband SSEP amplitudes below 0.5 µV died, had severe histopathological HIE, or were discharged with a severe clinical HIE leading to CPC 4 (Endisch et al., 2015). Median cortical broadband SSEP amplitudes in CPC 1 patients were 3.2 µV (2.5 – 4.7), 3.0 µV (1.8 – 4.0) in CPC 2 and 2.1 µV (1.3 – 2.9) in CPC 3 patients compared to 0.4 µV (0.1 – 0.8) in CPC 4 patients (Endisch et al., 2015). These SSEP amplitude findings were extended in recent study (Petzinka et al., 2018) from our institution investigating 61 CA patients who were discharged with a CPC 4 and showed no long-term improvement during follow-up with available SSEP recordings in 35 patients. The median cortical broadband SSEP amplitude in these patients was 0.29 µV (0 – 0.67) and 14 of 35 patients (40 %) showed bilaterally absent cortical SSEPs and further 4 patients amplitudes ≤ 0.3 µV. Hence 18 (51.4 %) of included CA patients with clinically proven severe HIE upon ICU discharge and during long-term follow-up either had bilaterally absent or low-amplitude cortical broadband SSEPs. The distribution of SSEP

amplitudes especially in patients with poor outcome and clinically proven severe HIE has been corroborated in recent studies (Choi et al., 2017; Carrai et al., 2019; Glimmerveen et al., 2019; Oh et al., 2019; Barbella et al., 2020) some of which did not perform therapy withdrawal and hence the poor outcome patients were unbiased by WLST. For instance, Barbella et al. (Barbella et al., 2020) found a median cortical broadband SSEP amplitude of 0.59 µV (0 – 7.64) in CPC 4 – 5 patients compared to 2.72 µV (0.45 – 11.82) in CPC 1 – 3 patients, Choi et al. (Choi et al., 2017) a mean cortical broadband SSEP amplitude of 1.33 µV in CPC 3 – 5 patients compared to 2.48 µV in CPC 1 – 2 patients, and Carrai et al. (Carrai et al., 2019) a mean cortical broadband SSEP amplitude of 0.50 µV in patients with Glasgow Outcome Scale (GOS) 1 compared to 0.98 µV in GOS 2 and 5.42 µV in GOS 5 patients.

A pathophysiological hypothesis of these findings supported by our brain autopsy study (Endisch et al., 2020) is that more severe HIE is associated with increased neuronal death in the cerebral cortex. As cortical SSEPs reflect a summation of postsynaptic electrical activity of the somatosensory cortex after thalamocortical input (Cruccu et al., 2008; Ozaki and Hashimoto, 2011; Putten, 2012), it is plausible that a decreasing number of functional cortical neurons may generate lower cortical SSEP amplitudes ultimately leading to bilaterally absent cortical SSEPs.

Moreover, a lower cortical broadband SSEP threshold provided higher sensitivities to predict poor outcome. A threshold of 0.62 µV increased the sensitivity for prediction of poor outcome from 30 % to 57 % compared to prediction by bilaterally absent cortical SSEPs in study 1 (Endisch et al., 2015) and was up to 74.5 % using a threshold of 0.64 µV in recent study (Oh et al., 2019) on 192 CA patients. However, sensitivities may depend on different study criteria to perform SSEP recordings for neuroprognostication.

Our results have decisively extended the prognostic value of SSEP recordings aside the well-known presence-absence-dichotomy of cortical potential. Treating physicians may not only use bilaterally absent cortical SSEPs but also low-amplitude cortical broadband SSEPs as an early prognostic parameter to predict severe HIE in comatose CA patients.

4.3 Cortical broadband SSEP amplitudes above 2.7 µV suggest absence of severe HIE

In contrast to previous studies (Bouwes et al., 2012; Nielsen et al., 2013), we discharged a relevant rate of CA patients with a clinical outcome of CPC 4 that comprises coma and an unresponsive wakefulness syndrome (Endisch et al., 2015). As survival with CPC 4 clinically defines severe HIE, CPC 4 patients may be more reliable to validate prognostic parameters unbiased by confounders compared to CPC 5 patients in whom extracerebral complications frequently lead to death (Dragancea et al., 2013; Endisch et al., 2015; Nobile et al., 2016).

Accordingly, cortical broadband SSEP amplitudes of 27 CPC 4 patients did not exceed 2.5 µV while 24 CPC 5 patients had cortical broadband SSEP amplitudes above 2.5 µV and 110 CPC 5 patients had a median cortical broadband SSEP amplitude of 0.5 µV (0 – 2.3) compared to 0.4 µV (0.1 – 0.8) in CPC 4 patients (Endisch et al., 2015). The overall clinical picture based on case reviews and other available neuroprognostication suggested absence of severe HIE in most patients with cortical broadband SSEP amplitudes above 2.5 µV.

This amplitude threshold was further corroborated by our brain autopsy findings that deceased CA patients with cortical broadband SSEP amplitudes above 2.7 µV frequently temporarily regained consciousness prior to death and all patients showed no/mild histopathological HIE considering confounders (Endisch et al., 2020). Moreover, we found in a recent study on CA patients surviving long-term with CPC 4 that only one of 35 CPC 4 patients (2.9 %) had cortical broadband SSEP amplitudes above 2.5 µV (Petzinka et al., 2018). An external validation of this upper cortical broadband SSEP amplitude threshold in CA patients with clinically proven severe HIE has been provided recently (Choi et al., 2017; Carrai et al., 2019; Oh et al., 2019; Barbella et al., 2020). Oh et al. (Oh et al., 2019) found that none of 16 CPC 4 patients had cortical broadband SSEP amplitudes above 2.31 µV, the one CPC 4 patient in Barbella et al. (Barbella et al., 2020) showed a cortical broadband SSEP amplitude below 2.0 µV, only two of 27 patients (7.4 %) with GOS 2 had a cortical broadband SSEP amplitude above 2.5 µV in Carrai et al. (Carrai et al., 2019), and in Choi et al. (Choi et al., 2017), only one of eight CPC 3 – 5 patients (12.5 %) showed cortical broadband SSEP amplitude above 2.5 µV.

These findings indicate that cortical broadband SSEP amplitudes above 2.7 µV suggest absence of severe HIE in CA patients considering rare exceptions and should prompt continuation of intensive care treatment and further neuroprognostication in CA patients with inconclusive prognostic parameter constellations. As a consequence of our findings, we have implemented an upper cortical broadband SSEP amplitude threshold for neuroprognostication in our institutional standard operating structure for multimodal neuroprognostication in comatose CA patients (Storm et al., 2019). Furthermore, in the recent guideline of the German Neurological Society (DGN) (Bender et al., 2018) on hypoxic-ischemic encephalopathy, cortical broadband SSEP amplitude are discussed as a new prognostic parameter and an upper cortical broadband SSEP amplitude threshold is incorporated in the multimodal neuroprognostication algorithm to predict absence of severe HIE. However, it is important that even further prospective studies on SSEP amplitudes corroborate and establish the prognostic value for the discussed upper and lower threshold of cortical broadband SSEP amplitudes in clinical routine to predict good and poor outcome in a multimodal neuroprognostication approach.

4.4 Extending the SSEP frequency spectrum for neuroprognostication in CA patients

To the best of our knowledge, we studied for the first time non-invasively high-frequency (600 Hz) SSEP components of comatose CA patients with a non-custom-designed SSEP device (Endisch et al., 2016). Previous human studies on high-frequency SSEPs were mainly performed on healthy subjects in experimental settings situated in electromagnetically shielded environments (Ozaki and Hashimoto, 2011; Fedele et al., 2012, 2015), recorded with low-noise amplifier custom-built SSEP devices (Scheer et al., 2011; Waterstraat et al., 2012, 2015) and included only limited patient numbers (Restuccia et al., 2003; Insola et al., 2004; Gobbelé et al., 2008b). Surprisingly, the disease-related changes of high-frequency SSEP components have hitherto been investigated in only few human studies (Coppola et al., 2005; Gobbelé et al., 2008b; Ooba et al., 2010; Ozaki and Hashimoto, 2011).

In a large study (Endisch et al., 2016) on 302 CA patients, we demonstrated that recording of high-frequency (600 Hz) SSEP components is feasible with surprisingly high quality despite an ICU environment with considerable electromagnetic interference. Furthermore, we found that late high-frequency (600 Hz) SSEP component amplitudes above 70 nV suggest absence of severe HIE incompatible with regain of consciousness. Importantly, high cortical broadband SSEP amplitudes were associated with high late high-frequency (600 Hz) SSEP component amplitudes. Our results hereby support previous findings showing that consciousness-related neuronal circuits substantially modulate amplitudes of late high-frequency SSEP components (Halboni et al., 2000; Ozaki and Hashimoto, 2011; Götz et al., 2015). The pathophysiological hypothesis for the prognostic value of late high-frequency (600 Hz) SSEP component is that it reflects postsynaptic high-frequency spiking activity in the somatosensory cortex and hence indicate an intact corticocortical synaptic integrity which is a prerequisite for regain of consciousness (Ozaki and Hashimoto, 2011; Putten, 2012).

Our findings hence suggest that late high-frequency (600 Hz) SSEP component amplitudes above 70 nV may serve as one of few other prognostic parameters (Rossetti et al., 2009; Endisch et al., 2015; Streitberger et al., 2017; Admiraal et al., 2019; Ruijter et al., 2019) to early predict absence of severe HIE in CA patients. However, more studies investigating high-frequency SSEP components in pathological conditions and after CA are needed before recommending a routine clinical usage of late high-frequency (600 Hz) SSEP component amplitudes.

4.5 No evidence for a self-fulfilling prophecy using bilaterally absent cortical SSEPs in multimodal neuroprognostication

Neuroprognostication studies are potentially susceptible to a self-fulfilling prophecy if the investigated prognostic parameters are used in WLST decisions (Greer et al., 2014; Rossetti et al., 2016). To minimize the potential risk of a self-fulfilling prophecy for one prognostic parameter, neuroprognostication at our institution followed the international guideline recommendations of a multimodal neuroprognostication algorithm (Leithner et al., 2012; Sandroni et al., 2014; Callaway et al., 2015).

We provided evidence against a self-fulfilling prophecy for bilaterally absent cortical SSEP as all patients with this prognostic parameter had poor outcome upon ICU discharge (Endisch et al., 2015) or in long-term (Petzinka et al., 2018), none regained consciousness during the ICU stay (Endisch et al., 2015, 2020) and all deceased patients showed severe histopathological HIE with pronounced neuronal death in the cerebral cortex (Endisch et al., 2020). The same applies for cortical broadband SSEP amplitudes below 0.5 µV. In other words, the prognostic value of bilaterally absent cortical SSEPs should have been critically questioned and a self-fulfilling prophecy discussed if we had found deceased CA patients with bilaterally absent cortical SSEPs but no/mild histopathological HIE in brain autopsy. Importantly, cortical broadband SSEP amplitudes were not a prognostic parameter in our previous multimodal neuroprognostication algorithm (Leithner et al., 2012; Storm et al., 2019) indicating that confounding by WLST decisions is unlikely. A self-fulfilling prophecy for bilaterally absent cortical SSEP could be bypassed if intensive care treatment is always continued but may cause ethical concerns due to the high rate of CA patients surviving with severe long-term HIE (Kim et al., 2016). In all recent studies with legal restrictions forbidding therapy withdrawal (Kim et al., 2018; Carrai et al., 2019; Oh et al., 2019; Scarpino et al., 2019), bilateral absence of cortical SSEPs have been exclusively associated with poor outcome corroborating the prognostic reliability to predict poor outcome.

However, the rare exceptions of CA patients surviving with good outcome despite bilaterally absent cortical SSEPs have to be kept in mind prior to WLST decisions (Leithner et al., 2010; Bender et al., 2012; Arch et al., 2014; Pfeiffer et al., 2014) and highlight the importance not to use a single prognostic parameter but to follow a multimodal neuroprognostication algorithm (Sandroni et al., 2014; Callaway et al., 2015; Bender et al., 2018; Storm et al., 2019) and to consider possible confounders.

4.6 Study limitations

Although we have performed to the best of our knowledge the largest retrospective histopathological study on CA patients with prognostic parameters and brain autopsy, only few deceased CA patients underwent brain autopsies. Due to the retrospective study design a potential selection bias for brain autopsies remains hence unclear and whether our results can be extended to the entire cohort of deceased CA patients. Future prospective studies should therefore aim to increase the rate of brain autopsies in deceased CA patients. Our decision to dichotomize brain autopsy patients histopathologically into no/mild HIE and severe HIE was based on an analysis on temporary regain of consciousness. However, we cannot completely exclude relevant functional outcome improvement in severe histopathological HIE in case of long-term survival. Conversely, no/mild HIE patients may comprise patients with some cortical neuronal death but below 30 % and hence we cannot certainly predict whether these CA patients would regain consciousness in long-term had they survived. Future histopathological studies may hence use additional analysis tools and different staining to study other cell types and corticocortical integrity. Due to local legal restrictions, we had to determine CPC outcome scores upon ICU discharge in our SSEP studies. However, CA patients discharged to rehabilitation may profoundly improve in clinical outcome (Estraneo et al., 2013; Howell et al., 2013). Although the median duration of ICU stay was 27 – 30 days in our CPC 4 patients (Endisch et al., 2015, 2016; Petzinka et al., 2018) and most CPC 4 patients died after hospital discharge using information of the state death register (Petzinka et al., 2018), a long-term clinical outcome with follow-up three and six months after CA would have been desirable. This methodological limitation in clinical outcome determination needs to be considered. We focused on the analysis of cortical broadband short-latency SSEP amplitudes. However, late-latency amplitudes of cortical broadband SSEPs may provide further prognostic value as previously shown (Zandbergen et al., 2006b) and should be studied in future prospective studies. In our institution, we recorded SSEPs using a non-custom-designed SSEP device with an amplifier noise of 14.7 nV/√Hz (Endisch et al., 2015, 2016). Although below currently recommended technical prerequisites (Scheer et al., 2011), further reduction of electrical noise levels of SSEP devices would improve signal-to-noise ratios of SSEP recordings and may slightly change SSEP amplitude thresholds (Scheer et al., 2006; Waterstraat et al., 2015). These technical details highlight again the importance to reduce noise levels during SSEP recordings and further develop low-noise SSEP devices.

5. Conclusion

In conclusion, the present thesis provides evidence that cortical noise levels during SSEP recordings should not exceed 0.5 µV to avoid the false classification of bilaterally absent cortical SSEPs in CA patients with good clinical outcome. Bilaterally absent cortical SSEPs and low-amplitude cortical broadband SSEP amplitudes below 0.5 µV were reliable prognostic parameters to predict severe HIE based on clinical outcome and brain autopsy. Histopathological results of brain autopsies argue against a self-fulfilling prophecy in current clinical practice to use SSEPs in a multimodal neuroprognostication algorithm. Cortical broadband SSEP amplitudes above 2.7 µV indicate absence of severe HIE based on clinical outcome and brain autopsy. Non-invasive recording of high-frequency (600 Hz) SSEP components is feasible in an ICU setting and late high-frequency SSEP component amplitudes above 70 nV may also suggest absence of severe HIE.

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Statutory Declaration

"I, Christian Endisch, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "Cortical somatosensory evoked potential amplitudes and severity of hypoxic-ischemic encephalopathy after cardiac arrest", independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

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Date Signature of doctoral candidate

Declaration of your own contribution to the publications

Christian Endisch contributed the following to the below listed publications:

Study 1:

Christian Endisch, Christian Storm, Christoph J. Ploner, Christoph Leithner, Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study, Neurology 2015; 85(20): 1752-60

Impact Factor: 8.689

(ranked 10th/199 journals in the Journal Citation Report 2018 "Clinical Neurology")

Contributions: Independent data acquisition under supervision of Christoph Leithner with collection and digitalization of SSEP recordings and completing baseline characteristics and recording conditions; complete data analysis together with Christoph Leithner including evaluation of SSEPs, determination of cortical noise levels and SSEP amplitudes, statistical analysis and independent creation of all figures and tables and case reviews of exceptional patients; complete data interpretation with Christoph Leithner and with help of Christoph Leithner and after critical discussions with other coauthors drafting and revision of the manuscript.

Study 2:

Christian Endisch, Gunnar Waterstraat, Christian Storm, Christoph J. Ploner, Gabriel Curio, Christoph Leithner, Cortical somatosensory evoked high-frequency (600 Hz) oscillations predict absence of severe hypoxic encephalopathy after resuscitation, Clinical Neurophysiology 2016; 127(7): 2561-9

Impact Factor: 3.675

(ranked 51st/199 journals in the Journal Citation Report 2018 "Clinical Neurology")

Contributions: Independent study conception and design; independent data acquisition with collection and digitalization of SSEP recordings and completing baseline characteristics and recording conditions; complete data analysis with Christoph Leithner including amplitudes of broadband SSEPs and high-frequency SSEP components and recording conditions, statistical analysis and independent creation of all figures and tables and case reviews of

exceptional patients; together with Christoph Leithner, Gabriel Curio and Gunnar Waterstraat and after critical discussions with other coauthors complete data interpretation, drafting and revision of the manuscript.

Study 3:

Christian Endisch, Erik Westhall, Martin Kenda, Kaspar J. Streitberger, Hans Kirkegaard, Werner Stenzel, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner, Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest, JAMA Neurol 2020; (Epub ahead of print), doi:10.1001/jamaneurol.2020.2340

Impact Factor: 12.321

(ranked 5th/199 journals in the Journal Citation Report 2018 "Clinical Neurology")

Contributions: Complete study conception and design with Christoph Leithner and Elisabet Englund; independent data acquisition in Lund, Sweden, and Århus, Denmark, including collection and completing baseline characteristics, case reviews, prognostic parameters and histopathological samples; complete data analysis of prognostic parameters supervised by Christoph Leithner, independent histopathological analysis of all patients in Berlin and Århus after histopathological teaching by Elisebet Englund in Lund, complete statistical analysis with Christoph Leithner and independent creation of all figures and tables and case reviews of exceptional patients; together with Christoph Leithner and Elisabet Englund and after critical discussion with other coauthors complete data interpretation, drafting and revision of the manuscript.

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Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

Study 1

Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study

Christian Endisch, Christian Storm, Christoph J. Ploner, Christoph Leithner

Neurology 2015; 85(20): 1752-60

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Supplementary material of study 1

Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study

Christian Endisch, Christian Storm, Christoph J. Ploner, Christoph Leithner

Neurology 2015; 85(20): 1752-60

https://doi.org/10.1212/WNL.0000000000002123

Study 2

Cortical somatosensory evoked high-frequency (600Hz) oscillations predict absence of severe hypoxic encephalopathy after resuscitation

Christian Endisch, Gunnar Waterstraat, Christian Storm, Christoph J. Ploner, Gabriel Curio, Christoph Leithner

Clinical Neurophysiology 2016; 127(7): 2561-9

https://doi.org/10.1016/j.clinph.2016.04.014

Supplementary material of study 2

Cortical somatosensory evoked high-frequency (600Hz) oscillations predict absence of severe hypoxic encephalopathy after resuscitation

Christian Endisch, Gunnar Waterstraat, Christian Storm, Christoph J. Ploner, Gabriel Curio, Christoph Leithner

Clinical Neurophysiology 2016; 127(7): 2561-9

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Study 3

Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest

Christian Endisch, Erik Westhall, Martin Kenda, Kaspar J. Streitberger, Hans Kirkegaard, Werner Stenzel, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner

JAMA Neurol 2020; 77(11): 1430-1439

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Supplementary material of study 3

Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest

Christian Endisch, Erik Westhall, Martin Kenda, Kaspar J. Streitberger, Hans Kirkegaard, Werner Stenzel, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner

JAMA Neurol 2020; 77(11): 1430-1439

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Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

List of peer-review publications

Publications

Hypoxic-ischemic encephalopathy evaluated by brain autopsy and neuroprognostication after cardiac arrest,
Christian Endisch, Erik Westhall, Martin Kenda, Kaspar J. Streitberger, Hans Kirkegaard, Werner Stenzel, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner,
JAMA Neurol 2020; (Epub ahead of print), doi:10.1001/jamaneurol.2020.2340

Awarded with "Paper of the Month 07/2020" by the Center for Stroke Research Berlin

Impact Factor: 12.321

(ranked 5th/199 journals in the Journal Citation Report 2018 "Clinical Neurology")

Timing of brain computed tomography and accuracy of outcome prediction after cardiac arrest,
Kaspar J. Streitberger, Christian Endisch, Christoph J. Ploner, Robert Stevens, Michael Scheel, Martin Kenda, Christian Storm, Christoph Leithner,
Resuscitation 2019; 145: 8-14.

Impact Factor: 4.572

(ranked 7th/33 journals in the Journal Citation Report 2018 "Critical Care Medicine")

Unresponsive wakefulness or coma after cardiac arrest – A long-term follow-up study,
Victor N. Petzinka, Christian Endisch, Kaspar J. Streitberger, Farid Salih, Christoph J. Ploner, Christian Storm, Jens Nee, Christoph Leithner,
Resuscitation 2018; 131: 121-127

Awarded with "Paper of the Month 07/2018" by the Center for Stroke Research Berlin

Impact Factor: 4.572

(ranked 7th/33 journals in the Journal Citation Report 2018 "Critical Care Medicine")

View-Independent Working Memory Representations of Artificial Shapes in Prefrontal and Posterior Regions of the Human Brain,

Thomas B. Christophel, Carsten Allefeld, Christian Endisch, John-Dylan Haynes,

Cerebral Cortex 2018; 28(6): 2146-2161

Impact Factor: 5.437

(ranked 45th/267 journals in the Journal Citation Report 2018 "Neuroscience")

Cortical somatosensory evoked high-frequency (600Hz) oscillations predict absence of severe hypoxic encephalopathy after resuscitation,

Christian Endisch, Gunnar Waterstraat, Christian Storm, Christoph J. Ploner, Gabriel Curio, Christoph Leithner,

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Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study.

Christian Endisch, Christian Storm, Christoph J. Ploner, Christoph Leithner,

Neurology 2015; 85(20): 1752-60

Awarded with "Paper of the Month 10/2015" by the Center for Stroke Research Berlin

Impact Factor: 8.689

(ranked 10th/199 journals in the Journal Citation Report 2018 "Clinical Neurology")

Cumulative Impact Factor as first author: 24.685

Cumulative Impact Factor as co-author: 14.581

Oral talks

09/2017 Prognostication of severity of hypoxic-ischemic encephalopathy evaluated by brain autopsies,
Christian Endisch, Erik Westhall, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Hans Friberg, Kaspar J. Streitberger, Elisabet Englund, Christoph Leithner,
3rd International Symposium on Post Cardiac Arrest, Lund, Sweden

02/2017 Hypoxisch-ischämische Enzephalopathie nach Reanimation – Evaluation prognostischer Parameter anhand von Autopsien,
Christian Endisch, Christoph Leithner, Christian Storm, Christoph J. Ploner, Kaspar J. Streitberger,
34th Arbeitstagung NeuroIntensivMedizin (ANIM), Vienna, Austria

10/2016 Severity of hypoxic encephalopathy after cardiac arrest: Prognostic parameters evaluated by brain autopsies,
Christian Endisch, Christoph Leithner, Christian Storm, Christoph J. Ploner, Kaspar J. Streitberger,
89th German Society of Neurology Congress (DGN), Mannheim, Germany

Poster presentations

01/2019 Die Rolle von Blutdruck und Herzfrequenz bei der hypoxisch-ischämischen Enzephalopathie nach Herzstillstand und erfolgreicher Reanimation: Eine retrospektive Studie an 354 Reanimationspatienten mit Hirnautopsie,

Christian Endisch, Sandra Preuß, Christian Storm, Christoph J. Ploner, Christoph Leithner,
36th Arbeitstagung NeuroIntensivMedizin (ANIM), Berlin, Germany

09/2018 Bypassing the self-fulfilling prophecy of prognostic parameters after cardiac arrest: Severity of hypoxic-ischemic encephalopathy evaluated by brain autopsies,

Christian Endisch, Erik Westhall, Josche Streitberger, Birger Johnsen, Christian Storm, Christoph Ploner, Tobias Cronberg, Hans Friberg, Elisabet Englund, Christoph Leithner,
16th Neurocritical Care Society Meeting (NCS), Boca Raton, USA

05/2018 The prognostic value of median nerve SSEP after cardiac arrest: Evaluation of severity of hypoxic-ischemic encephalopathy by brain autopsies,
Christian Endisch, Erik Westhall, Birger Johnsen, Christian Storm, Christoph J. Ploner, Tobias Cronberg, Elisabet Englund, Christoph Leithner,
31st International Congress of Clinical Neurophysiology (ICCN), Washington D.C., USA

04/2017 Severity of brain injury after global ischemia: Prognostic parameters of cardiac arrest survivors evaluated by brain autopsies,
Christian Endisch, Christoph Leithner, Christian Storm, Christoph J. Ploner, Kaspar J. Streitberger, BRAIN and BRAIN PET 2017 Conference, Berlin, Germany

06/2015 Amplitudes of SSEP after cardiac arrest and targeted temperature management: a prospective reevaluation,
Christian Endisch, Christian Storm, Christoph J. Ploner, Christoph Leithner,
2nd Postresuscitation Care Meeting, Lund, Sweden

Awarded with a traveling grant by the Felgenhauer Foundation

Median nerve somatosensory evoked high-frequency oscillations for prognostication of good neurological outcome in posthypoxic coma,
Christian Endisch, Gunnar Waterstraat, Christian Storm, Christoph J. Ploner, Gabriel Curio, Christoph Leithner,
2nd Postresuscitation Care Meeting, Lund, Sweden

03/2015 Amplitudes of cortical somatosensory evoked potentials and outcome prediction after cardiac arrest,
Christian Endisch, Christoph J. Ploner, Christian Storm, Christoph Leithner,
35th International Symposium on Intensive Care and Emergency Medicine (ISICEM), Bruxelles, Belgium

Awarded with the Poster Award

Somatosensory evoked high-frequency oscillations and prognostication after cardiac arrest,
Christian Endisch, Christoph J. Ploner, Christian Storm, Christoph Leithner,
35th International Symposium on Intensive Care and Emergency Medicine (ISICEM), Bruxelles, Belgium

01/2015 Somatosensorisch evozierte kortikale hochfrequente Oszillationen bei Patienten nach Herzstillstand und Reanimation,
Christian Endisch, Christoph J. Ploner, Christian Storm, Christoph Leithner,
32nd Arbeitstagung NeuroIntensivMedizin (ANIM), Berlin, Germany

Awarded with the 3. Poster Award

Amplituden der kortikalen Medianus-SEP und neurologisches Outcome von Patienten nach Herzstillstand und Hypothermie – eine prospektive Re-Evaluation,
Christian Endisch, Christoph J. Ploner, Christian Storm, Christoph Leithner,
32nd Arbeitstagung NeuroIntensivMedizin (ANIM), Berlin, Germany

03/2014 SSEP revisited – the significance of absolute N20 amplitudes for prognosis following cardiac arrest,
Christian Endisch, Christoph J. Ploner, Christian Storm, Christoph Leithner,
30th International Congress of Clinical Neurophysiology (ICCN), Berlin, Germany

05/2013 Decoding invariant representations in visual working memory,
Thomas B. Christophel, Christian Endisch, John-Dylan Haynes,
13th Vision Sciences Society Meeting, Naples, USA

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