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Clinical paper

Early recovery of frontal EEG slow wave activity during propofol sedation predicts outcome after cardiac arrest

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Abstract

Aim of the study: EEG slow wave activity (SWA) has shown prognostic potential in post-resuscitation care. In this prospective study, we investigated the accuracy of continuously measured early SWA for prediction of the outcome in comatose cardiac arrest (CA) survivors.

Methods: We recorded EEG with a disposable self-adhesive frontal electrode and wireless device continuously starting from ICU admission until 48 h from return of spontaneous circulation (ROSC) in comatose CA survivors sedated with propofol. We determined SWA by offline calculation of C-Trend® Index describing SWA as a score ranging from 0 to 100. The functional outcome was defined based on Cerebral Performance Category (CPC) at 6 months after the CA to either good (CPC 1–2) or poor (CPC 3–5).

Results: Outcome at six months was good in 67 of the 93 patients. During the first 12 h after ROSC, the median C-Trend Index value was 38.8 (interquartile range 28.0–56.1) in patients with good outcome and 6.49 (3.01–18.2) in those with poor outcome showing significant difference ($p < 0.001$) at every hour between the groups. The index values of the first 12 h predicted poor outcome with an area under curve of 0.86 (95% CI 0.61–0.99). With a cutoff value of 20, the sensitivity was 83.3% (69.6%–92.3%) and specificity 94.7% (83.4%–99.7%) for categorization of outcome.

Conclusion: EEG SWA measured with C-Trend Index during propofol sedation offers a promising practical approach for early bedside evaluation of recovery of brain function and prediction of outcome after CA.

Keywords: Cardiac arrest, EEG, Hypoxic-Ischemic encephalopathy, Outcome, Prognostication, Propofol

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Introduction

Hypoxic-ischemic encephalopathy (HIE) is the leading cause of death and poor outcome after intensive care unit (ICU) admission following cardiac arrest (CA).[1,2] The guidelines of European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM)[3] as well as American Heart Association (AHA)[4] suggest multimodal approach for outcome prediction in post-resuscitation care including clinical examination, electrophysiologic measurements, biomarkers and neuroimaging. Accurate prognostication is essential to avoid inappropriate withdrawal of life-sustaining therapies and, on the other hand, futile treatment. In addition to these ethically important aspects in quality of care, increased accuracy in outcome prediction following CA has been associated with economic benefits in societal level.[5]

Electroencephalogram (EEG) is the most commonly used modality to provide prognostic information supporting clinical examination after CA.[6] Specific EEG features have shown strong time-dependent association with outcome.[7,8] While there is ongoing debate whether continuous or brief intermittent EEG recording is optimal,[9,10] there is clear evidence that most valuable prognostic information provided by EEG is gained during the first 24 h after CA.[11,12]

Despite the clear recommendations, real world utilization of EEG in the early post-resuscitation care is still rare.[13] Low adherence to consensus guidelines may result from several reasons including low availability of qualified technicians and high costs related to carrying out recordings especially outside office hours.[14,15] Furthermore, lack of experts with adequate training to interpret intensive care recordings may restrict the use of EEG in post-resuscitation care.[16]

We have recently evaluated EEG slow wave activity (SWA) for outcome prediction in comatose CA survivors.[17] Slow waves (<1 Hz) are the most important EEG signatures of non-rapid eye movement sleep also occurring during general anesthesia.[18,19] In our experimental pilot study, the patients with poor outcome were unable to generate SWA during controlled propofol sedation at 48 h after CA.[17] Further exploration of the data showed that the SWA was sufficiently captured by a reduced frontal electrode set.[20]

In this prospective multicenter study, we investigated the accuracy of EEG SWA in predicting the outcome of comatose CA survivors during propofol sedation. We hypothesized that low SWA during propofol sedation in the first 48 h after CA would be associated with poor outcome. The objective of the study was to investigate this association with an approach clinically suitable for ICU environment including a practical continuous EEG recording and automatic parametrization of SWA.

Methods

Study design and data collection

This was a prospective observational study (NCT03485781) carried out in two University Hospital ICUs. Patients were enrolled from the 1st of October 2017 to the 31st of January 2019 in Helsinki and Oulu University Hospitals. Ethical approval was obtained from the Ethical Committee of North Ostrobothnia's Hospital District (117/2016). A delayed consent approach was used. A written informed consent was obtained from the patient's next of kin as soon as possible after inclusion to the study and from all patients who regained sufficient cognitive capacity. Eligibility to the study was evaluated on admission to the ICU. In Helsinki, all consecutive patients were included, whereas in Oulu patients were included during office hours. We included adult (≥18 years) patients that remained unconscious after out-of-hospital CA and return of spontaneous circulation (ROSC) treated in the participating ICUs. We included patients with both shockable and non-shockable initial rhythms. Exclusion criteria included significant pre-existing neurological comorbidity (e.g. Alzheimer's disease, poorly controlled epilepsy or stroke with significant functional impairment), foreign citizens, pregnant or lactating patients, patients under coercive measures or if probability of obtaining informed consent was anticipated small.

Clinical protocol

The patients were treated according to local protocols in accordance with published international guidelines.[3,4] In Helsinki, patients with shockable rhythm received target temperature management (TTM) for 24 h at 33 °C. In Oulu, TTM at 36 °C was applied regardless of the initial rhythm. In case of hemodynamic instability, target temperature was allowed to be increased from 33 °C to 34–36 °C. The patients were cooled using an intravascular device and rewarmed slowly at a controlled rate of 0.25 °C/h. Propofol was used for sedation as needed at a maximum dose of 4 mg/kg/h. Pain and shivering were treated with opioids and muscle relaxants based on clinicians' discretion. Use of midazolam or other benzodiazepines were not encouraged during the EEG recording. Propofol infusion was discontinued at the end of TTM when normothermia was achieved (≥36 °C). We recorded use of propofol during the first 48 h after ROSC.

Both centers utilize a multimodal approach for prognostication of comatose CA patients. In patients who remain unconscious after TTM and rewarming, data obtained using computer tomography, magnetic resonance imaging, laboratory markers, sensory evoked potentials and standard EEG (20–30 min), in addition to careful clinical examination by an experienced neurologist are used for diagnosing HIE and decision for withdrawal of active life support, at a minimum time of 72 h from ROSC.

The patients were assigned to either good or poor outcome group based on their functional outcome. This was done using cerebral performance category (CPC) where CPC 1–2 represented good outcome and CPC 3–5 poor outcome. The score was determined 6 months after the CA via a telephone interview by an experienced neurologist blinded to the SWA data.

EEG slow wave activity

For measurement of SWA, a continuous EEG recording was initiated as soon as possible after admission to the ICU and continued until 48 h from ROSC. If the patient woke up before 48 h, the recording was stopped. The recording was carried out with a disposable self-adhesive BrainStatus electrode attached to the forehead of the patient including 10 EEG channels (Fp1, Fp2, Af7, Af8, F7, F8, Sp1, Sp2, T9, T10) and a wireless recording device (Bittium Oyj, Oulu, Finland). Electrode placement and initiation of recording was performed by a study nurse or trained ICU nurse according to written instructions. In case of need for electric cardioversion or radiological examinations of the brain, the personnel was instructed to detach the electrode from the recording device. All clinical personnel were blinded to the EEG recorded for the study which was carried out separately from the possible standard EEG recording needed for diagnostic purposes.

SWA was determined by offline calculation of C-Trend® Index (v.1.0.0.0, Cerenion, Oulu, Finland) from the continuous EEG recordings. C-Trend is a CE marked medical device software that utilizes artificial intelligence to capture several power and connectivity features in producing a parameter, C-Trend Index, of the SWA in EEG. The parameter ranges from 0 to 100 in values, values above 80 referring to high normal SWA seen during anesthesia and values below 50 referring to abnormal or low SWA. The calculation was made with the software version 1.0.0.0. No optimization or any other modification of the algorithm was made due to the study. While the values of C-Trend Index are calculated from approximately 60-s EEG sequences, average index values were also determined for each hour after ROSC for further analysis. Furthermore, average values of C-Trend Index were calculated also for each of the four 12-h time periods after ROSC (1–12 h, 13–24 h, 25–36 h, 37–48 h).

Statistical analysis

The number of patients included was set to 100 based on sample size calculations presented by Flahault et al.[21] Expecting 40% case frequency i.e. incidence of poor outcome and a specificity of 0.90 in predicting it, this sample size would result in a lower confidence interval (CI) limit of 0.70 for specificity, which was considered to be sufficient for the study.

We present categorical variables as counts and percentages and continuous variables as means and standard deviations (SDs) or medians and interquartile ranges (IQR). Average C-Trend Index values for each hour after ROSC were calculated and a linear mixed effects model with compound symmetry as covariance matrix was used to identify whether the values were different between patients with good and poor outcome. The analysis takes into account the repeated measurement of subjects over time and interaction between outcome and time. In case of significant effect of interaction, the values were compared between groups at different time points with the Mann-Whitney *U* test. The normality of distributions of index values was tested with the Kolmogorov–Smirnov test. We examined the accuracy of C-Trend Index in predicting poor outcome at six months after CA by calculating the area under curve (AUC) from receiver operating characteristic (ROC) curve. The accuracy was determined for each of the four 12-h time periods after ROSC (1–12 h, 13–24 h, 25–36 h, 37–48 h) by calculating the average C-Trend Index value over the entire time period. The 95% CIs for AUCs were defined with a bootstrapping method provided by Matlab's *perfcurve* function. Furthermore, we determined the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% CIs for the index cutoff values 20, 50, and 80 for the same time periods after ROSC. These cutoff values, provided by the manufacturer, represent change from abnormal or low SWA (<50) to moderate SWA (50–80) and further to high normal SWA (>80). Cutoff value 20 was chosen to indicate absent or highly abnormal SWA.

We conducted all statistical analyses with SPSS (SPSS, Chicago, IL, USA) version 24.0 and Matlab (The MathWorks Inc., Natick, MA, USA) version R2018a with Statistics and Machine Learning Toolbox version 11.3. Due to the multiple comparisons at different time points, the level of significance was set at p value less than 0.001.

Results

In total, the data from 93 patients were included in the study (Fig. 1). Patient characteristics, resuscitation-associated factors and treatment related information according to the outcome are given in Table 1

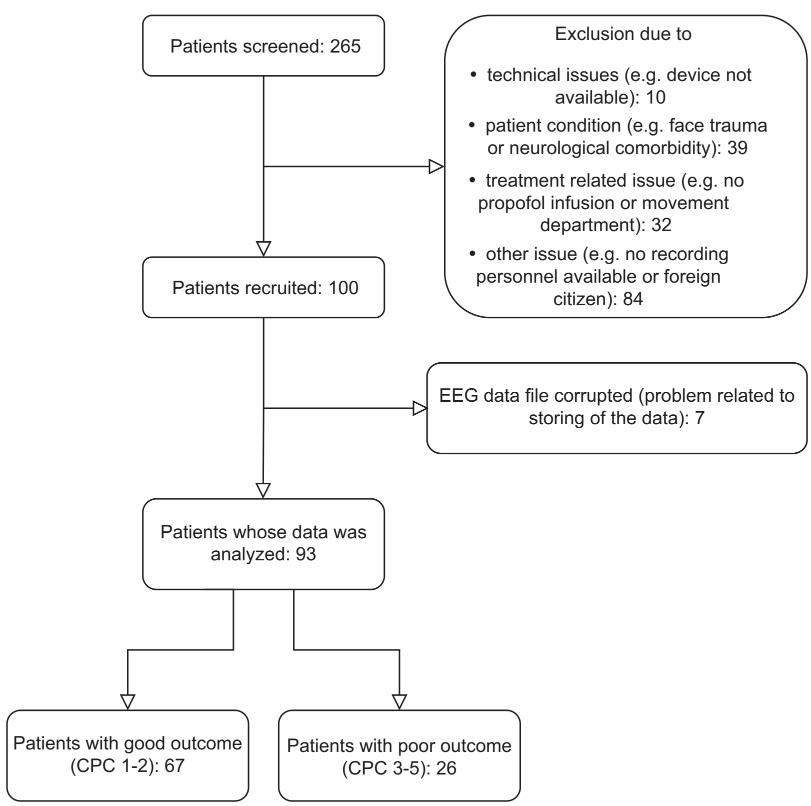

Fig. 1 – Flowchart of the study population.

Table 1 – Patient characteristics, resuscitation-associated factors and treatment related information according to outcome.

	All patients (N = 93)	Good outcome (N = 67)	Poor outcome (N = 26)
Age, years, mean (SD)	61.4 (12.9)	60.8 (12.9)	62.7 (12.9)
Sex, male, N (%)	79 (84.9)	55 (82.1)	24 (92.3)
Weight, kg, mean (SD)	84.5 (15.9)	84.0 (15.8)	85.8 (16.3)
Initial rhythm shockable, N (%)	79 (84.9)	61 (91.0)	18 (69.2)
ROSC, minutes, mean (SD)	19.2 (8.4)	17.7 (7.6)	22.9 (9.4)
TTM			
33 °C, N (%)	72 (77.4)	52 (77.6)	20 (76.9)
36 °C, N (%)	21 (22.6)	15 (22.4)	6 (23.1)
Mean dose of propofol during EEG, mg/kg/h, mean (SD)	2.95 (0.99)	3.05 (1.00)	2.71 (0.95)

SD standard deviation, *ROSC* return of spontaneous circulation, *TTM* target temperature management.

for patients whose EEG was analyzed. The functional outcome was poor (CPC 3–5) in 26 (28%) and good (CPC 1–2) in 67 (72%) patients after 6-month follow-up period. There were 25 deaths of which 19 (76%) were due to HIE. One patient recovered to CPC 3. Propofol infusion was used in all patients. The mean starting time for EEG recording was 9.01 (SD 9.08) hours after the ROSC and the mean recording duration was 27.7 (12.3) hours. The amount of EEG data and propofol infusion rates at different time points are provided in the Electronic Supplementary Material (ESM) Figure S2 and Figure S3, respectively.

Fig. 2 presents the C-Trend Index values, indicating the SWA, in patients with good and poor outcome during the first 48 h after ROSC. The time, outcome and their interaction had all significant ($p < 0.001$) effect on the values. While the median values in good outcome group were higher during the entire time-period, the difference is strongest in the beginning. During the first 12 h, the median C-Trend Index value was 38.8 (IQR 28.0–56.1) in patients with good outcome and 6.49 (3.01–18.2) in patients with poor outcome showing significant difference ($p < 0.001$) at every hour between the groups. Both groups represent increasing values, patients with poor outcome with steeper slope resulting in higher overlap between the groups towards the end of the evaluation period. Examples of the behavior of C-Trend Index on individual level are illustrated in Fig. 3 with four patients representing different characteristics of SWA recovery. Two of the patients (A and B) represent good outcome having moderate normal SWA (C-Trend Index >50) already from the beginning of the recording or before 12 h from ROSC. Two of the patients (C and D) represent poor outcome having a longer delay in the occurrence of SWA. Examples of EEGs from these patients with corresponding C-Trend Index values are given in Fig. 4. The recordings of patient A and C are illustrated in more detail in the ESM (Fig. S3 and Fig. S4).

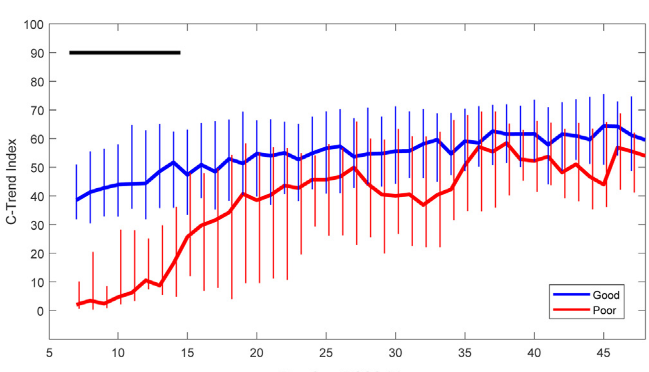

Fig. 2 – C-Trend Index values, representing EEG slow wave activity, in good and poor outcome patients. The thick red and blue lines represent group medians after return of spontaneous circulation (ROSC). Narrow vertical lines represent interquartile ranges. The thick black line on top indicates statistically significant ($p < 0.001$; Mann–Whitney *U* test used as Kolmogorov–Smirnov test suggested non-normal distribution) difference between groups at that specific time point (hour) after ROSC. The data before 7 h from ROSC is not presented due to low number of recordings (N < 50).

ROC curves and AUCs for predicting poor outcome were calculated based on average C-Trend Index values calculated over time periods of 1–12 h, 13–24 h, 25–36 h, and 37–48 h after ROSC (Fig. 5). The classification statistics including sensitivity, specificity, PPV, and NPV for index cutoff values 20, 50, and 80 are given in Table 2. The highest accuracy for predicting poor outcome is reached with the time period of 1–12 h in which the AUC is 0.86 (95% CI 0.61 –0.99) and, with cutoff value 20, the sensitivity and specificity are 83.3% (69.6%–92.3%) and 94.7% (83.4%–99.7%). The corresponding PPV is 83.3% (69.6%-92.3%) and NPV 94.7% (83.4%-99.7%). The classification performance decreases towards the end of the evaluation period which is due to more substantial increase of SWA in poor outcome group as shown already in Fig. 2.

Discussion

Our findings suggest association between early SWA and functional outcome in comatose CA survivors treated with TTM. The findings are in line with results of a previous pilot study indicating similar association during controlled propofol sedation at 48 h after ROSC.[17,20] In the current study, we show the association in a larger patient group with routine propofol sedation and continuously recorded SWA from the ICU admission until 48 h from ROSC. We also utilize an approach clinically suitable for ICU environment including a practical EEG recording and automatic parametrization of SWA using C-Trend Index. If validated in larger samples, this method may become a valuable additional tool for prognostication of CA patients, especially in settings without neurophysiology coverage or difficulty in obtaining intermittent EEG.

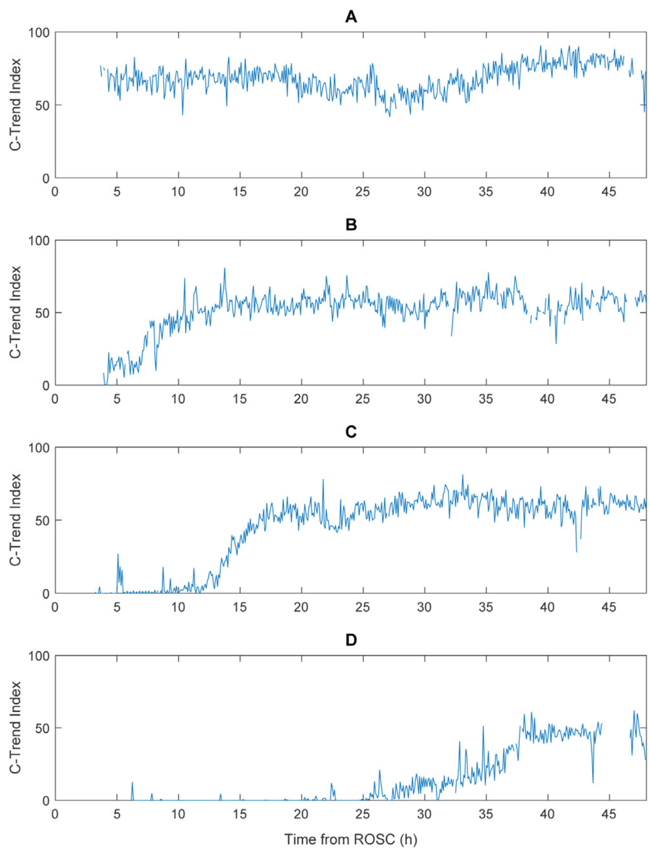

Fig. 3 – Behavior of C-Trend Index, representing EEG slow wave activity, in four different patients after return of spontaneous circulation (ROSC). (A) and (B) represent patients with good outcome and (C) and (D) patients with poor outcome.

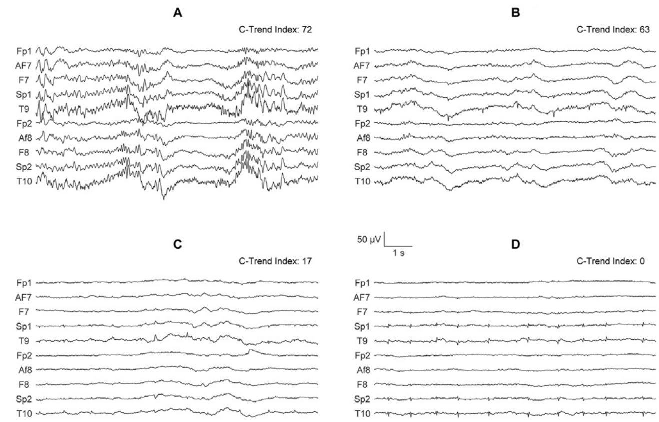

Fig. 4 – Examples of EEGs with corresponding C-Trend Index values. The examples are from the patients (A-D) presented in Fig. 3 and represent recordings at 11 h from return of spontaneous circulation. The C-Trend Index values decrease gradually from A to D indicating reduction in slow wave activity. Some ECG artifact is seen in the recordings B-D.

The results of the study indicate that SWA is most accurate in predicting the outcome during the early phase of recovery. The threshold value 20 for C-Trend Index, indicating highly abnormal or absent SWA, resulted in the best classification accuracy when applied to the average index values before 12 h from ROSC. To provide clear findings for clinical utilization of the C-Trend Index in multimodal prognostication, we also made the following observations based on the one-hour average C-Trend Index values of the first 24 h after ROSC:

1. if at least half of the values were below 20, the probability for poor outcome was 89%,
2. if at least half of the values were higher than 20, the probability for poor outcome was 11%,
3. if at least one value was higher than 80, the probability for poor outcome was 0%.

Similar time-dependency has been reported in previous studies investigating the predictive value of raw EEG features (e.g. burst suppression, signal continuity, diffuse slowing) after CA. Hofmeijer et al. found EEG to be accurate as a single measure and a robust contributor to multimodal prognostication, but only when the recordings before 24 h from ROSC were used.[12] Comparable results were published by Ruijter et al.[8] and Sivaraju et al.[21] who also reported EEG to be most accurate in predicting the outcome in the first 24 after CA.

Quantitative parameters integrating several EEG features have been used for predicting the outcome after CA also before this study.[22–26] The purpose of these parameters is similar to C-Trend Index: to simplify the interpretation of EEG and consequently make it more feasible in clinical use. In a recent study, a model comprising 52 EEG features was built for predicting the outcome after CA resulting in an accuracy of AUC 0.83.[22] Another parameter, cerebral recovery

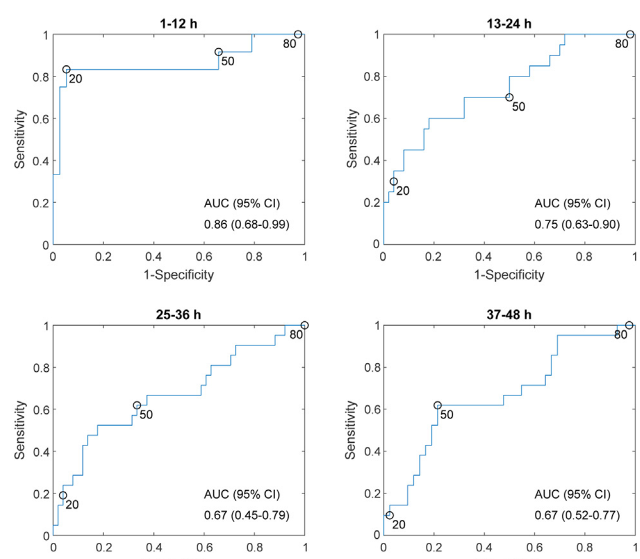

Fig. 5 – Receiver operating characteristic curve and area under the curve (AUC) for predicting poor outcome based on average C-Trend Index values. The statistics are calculated separately for periods 1–12 h, 13–24 h, 25–36 h, and 37–48 h after return of spontaneous circulation. The index cutoff values 20, 50, and 80 are indicated on the curve.

Table 2 – The classification statistics for the C-Trend Index values in predicting poor outcome at 6 months after cardiac arrest. The index values are averages calculated over the four different 12 -h time periods. Three different cutoff values are used for categorization of outcome.

Time from ROSC	AUC (95% CI)	C-Trend Index cutoff value	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1–12 h	0.86 (0.61–0.99)	20	83.3% (69.6%–92.3%)	94.7% (83.4%–99.7%)	83.3% (69.6%–92.3%)	94.7% (83.4%–99.7%)
		50	91.7% (79.5%–97.9%)	34.2% (21.8%–48.9%)	30.6% (18.7%–45.1%)	92.9% (81.0%–98.6%)
		80	100% (91.1%–100%)	2.6% (0.2%–11.8%)	24.5% (13.9%–38.7%)	100% (91.1%–100%)
13–24 h	0.75 (063–0.90)	20	30.0% (19.9%–42.2%)	96.0% (87.6%–99.7%)	75.0% (63.0%–84.4%)	77.4% (65.6%–86.4%)
		50	75.0% (63.0%–84.4%)	50.0% (37.9%–62.1%)	37.5% (26.5%–49.8%)	83.3% (72.1%–91.1%)
		80	100% (93.5%–100%)	2.0% (0.2%–8.8%)	29.0% (19.1%–41.1%)	100% (93.5%–100%)
25–36 h	0.67 (0.45–0.79	20	19.0% (11.1%–30.1%)	96.1% (87.8%–99.7%)	66.7% (54.5%–77.2%)	74.2% (62.4%–83.7%)
		50	61.9% (49.7%–72.9%)	64.7% (52.5%–75.4%)	41.9% (30.6%–54.1%)	80.5% (69.1%–88.8%)
		80	100% (93.7%–100%)	0.0% (0.1%–4.9%)	29.2% (19.3%–41.1%)	NA
37–48 h	0.67 (0.52–0.77	20	9.5% (3.9%–19.8%)	97.6% (89.1%–100%)	66.7% (53.6%–77.9%)	68.3% (55.3%–79.3%)
		50	61.9% (48.8%–73.7%)	78.6% (66.1%–87.8%)	59.1% (46.0%–71.1%)	80.5% (68.2%–89.3%)
		80	100% (92.8%–100%)	2.4% (0.3%–10.0%)	33.9% (22.7%–46.9%)	100% (92.8%–100%)

ROSC return of spontaneous circulation, *AUC* area under curve, *PPV* positive predictive value, *NPV* negative predictive value, *CI* confidence interval.

index (CRI), also integrating several EEG features, was reported to reach a maximum accuracy of AUC 0.92 in predicting the outcome after CA.[23] In both of these publications, the model presented was trained and validated based on the data collected in the study, not a model that would have been fixed already beforehand. In contrast, Bispectral (BIS) index, a parameter intended to aid in monitoring the anesthetic effect on EEG, has also been used for predicting the outcome after CA resulting in a maximum accuracy of AUC 0.72 –0.79.[24,25] Interestingly, both CRI and BIS seem to reach their best accuracy in outcome prediction also during the first 24 h after ROSC.

Wide clinical utilization of EEG as a part of multimodal prognostication requires a practical solution. The limited availability of qualified technicians to initiate the recording is one of the major reasons for the current rare use of EEG in post-resuscitation care.[13] Being most informative when performed early puts even more pressure on the EEG's immediate availability. While the practicality of the recording can be increased by reducing the number of EEG channels and focusing on the forehead region where the electrode is convenient to attach, this may have unfavorable effect of the prediction accuracy. For example, when full EEG cap was changed to a reduced frontotemporal montage, the maximum accuracy of CRI dropped to AUC 0.82.[27] In the current study, a reasonably good prediction accuracy was reached with a self-adhesive electrode suitable for long-term recording and possible to attach by ICU nurse. Combined with online calculation of C-Trend Index, the approach may provide a practical solution for real-time evaluation of brain function at the bedside.

The study has several limitations which should be addressed in future. Firstly, the sample size was rather small and confirming the results in a larger patient group would be beneficial. The small sample size and deviation from the expected case frequency (28% instead of 40%) reduce the level of confidence of the presented results. Including patients from two centers treated with TTM at both 33 °C and 36 °C could be, however, seen as a strength of the current study. Secondly, we did not investigate whether including SWA analysis would contribute to multimodal prognostication if applied together with clinical examination, radiological imaging, and biomarkers. Thirdly, the effect of previous conditions, potentially affecting brain function and EEG, on C-Trend Index should be investigated. These conditions, including stroke, trauma, and Alzheimer's disease, for example, may disturb the SWA and thus confound the interpretation of the index. In the current study, we also made an interesting incidental finding on how an epileptic seizure affects the C-Trend Index (see the ESM section "C-Trend Index and epileptic EEG activity") which should be further explored in future.

Conclusions

In this study, we found early recovery of SWA measured with C-Trend Index during propofol sedation to be associated with good outcome in comatose CA survivors. The outcome prediction was most accurate during the first 12 h after ROSC. If validated in larger samples, the method offers a promising practical approach for early bedside evaluation of recovery of brain function after CA potentially supplementing the multimodal prognostication especially in settings without neurophysiology coverage and difficulty obtaining intermittent EEG.

Conflict of interest

Jukka Kortelainen and Eero Väyrynen are co-founders of Cerenion Oy (Finland). Markus B Skrifvars reports lecture fees and travel grants from BARD Medical (Ireland).

CRediT authorship contribution statement

All authors contributed to the study conception and design. Data collection were performed by Jukka Kortelainen, Marjaana Tiainen, Daniel Strbian, Kirsi Rantanen, Jouko Laurila, Johanna Hästbacka and Juha Koskenkari. The analyses were performed by Jukka Kortelainen. The first draft of the manuscript was written by Jukka Kortelainen, Tero Ala-Kokko, and Johanna Hästbacka and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2021.05.032.

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