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EEG synchronization measures are early outcome predictors in comatose patients after cardiac arrest

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HIGHLIGHTS

- Predicting neurological outcome after cardiac arrest remains a challenging task.
- Bivariate EEG synchronization measures can contribute to early prognostication.
- Further studies are needed to evaluate the place of quantitative EEG within multi-modal prognostic algorithms.

ABSTRACT

Objective: Outcome prognostication in comatose patients after cardiac arrest (CA) remains a major challenge. Here we investigated the prognostic value of combinations of linear and non-linear bivariate EEG synchronization measures.
Methods: 94 comatose patients with EEG within 24 h after CA were included. Clinical outcome was assessed at 3 months using the Cerebral Performance Categories (CPC). EEG synchronization between the left and right parasagittal, and between the frontal and parietal brain regions was assessed with 4 different quantitative measures (delta power asymmetry, cross-correlation, mutual information, and transfer entropy). 2/3 of patients were used to assess the predictive power of all possible combinations of these eight features (4 measures × 2 directions) using cross-validation. The predictive power of the best combination was tested on the remaining 1/3 of patients.
Results: The best combination for prognostication consisted of 4 of the 8 features, and contained linear and non-linear measures. Predictive power for poor outcome (CPC 3–5), measured with the area under the ROC curve, was 0.84 during cross-validation, and 0.81 on the test set. At specificity of 1.0 the sensitivity was 0.54, and the accuracy 0.81.
Conclusion: Combinations of EEG synchronization measures can contribute to early prognostication after CA. In particular, combining linear and non-linear measures is important for good predictive power.
Significance: Quantitative methods might increase the prognostic yield of currently used multi-modal approaches.
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1. Introduction

Prognostication in comatose patients after cardiac arrest (CA) remains one of the biggest challenges for a neurologist in the intensive care unit (Rossetti et al., 2016). Current clinical decisions are based on a multi-modal approach including several clinical and para-clinical tests, one of the most important being Electroencephalography (EEG) (Horn et al., 2014; Rossetti et al., 2016;

Abbreviations: AP, anterior–posterior axis; AUC, area under the ROC curve; CA, cardiac arrest; CC, cross-correlation; CPC, Glasgow–Pittsburg Cerebral Performance Categories; LR, leftright axis; MI, mutual information; qEEG, quantitative electroencephalography; RDP, relative delta power; ROC, receiver operating characteristic curve; TE, transfer entropy; TTM, targeted temperature management.

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Sandroni et al., 2014). Several EEG patterns during hypothermia or controlled normothermia (summarized as targeted temperature management, TTM) have been associated with an unfavourable outcome (Hofmeijer et al., 2014, 2015; Sivaraju et al., 2015; Westhall et al., 2016), whereas an early, continuous (Hofmeijer et al., 2015) and reactive EEG (Sivaraju et al., 2015; Tsetsou et al., 2013) may herald a favourable outcome. However, clinical EEG also has several limitations. Firstly, it requires the assistance of a trained specialist for interpretation (Spalletti et al., 2016; Taccone et al., 2014). Secondly, it lacks objectivity as inter-rater agreement remains imperfect despite the attempt to propose standardized interpretations (Foreman et al., 2016; Halford et al., 2015; Hirsch et al., 2013; Ng et al., 2015; Westhall et al., 2016). In particular, the classification of visual EEG patterns into unfavourable, intermediate, or favourable categories varies between studies (Hofmeijer et al., 2015; Sivaraju et al., 2015; Westhall et al., 2015, 2016). Computer/algorithm-based analysis of EEG (quantitative EEG; qEEG) appears as a promising approach to circumvent these limitations.

Several univariate qEEG methods were used to assist visual interpretation, providing for instance compact representations of amplitude or spectrum of EEGs, allowing for rapid identifications of segments where the EEG signal changes. These methods have been used successfully for prognostication after CA (Moura et al., 2014; Oh et al., 2015; Rundgren et al., 2010). Various qEEG measures have been used to refine EEG patterns classifications, such as generalized periodic discharges (Ruijter et al., 2015), similarity of bursts in burst-suppression (Hofmeijer et al., 2014), burst-suppression ratio and epileptiform activity (Wennervirta et al., 2009), or reactivity (Noirhomme et al., 2014). Five different uni- and multivariate qEEG features were combined into a single index (“cerebral recovery index”) to mimic the way neurologists visually interpret EEG, serving as “surrogate electroencephalographers” (Tjepkema-Cloostermans et al., 2013).

Bivariate synchronization measures are classical tools for quantitative EEG analysis in the context of epilepsy or neurodegenerative diseases, where they are often used to define functional networks (Bullmore and Sporns, 2009; Stam and van Straaten, 2012). However, they have only been applied in very few studies for prognostication after CA. Coherence, for instance, was one of the elements of the cerebral recovery index mentioned above. In another study, a bivariate measure based on similarity of the power spectrum of EEG signals was used to define a functional graph, the properties of which were different according to the clinical outcome (Beudel et al., 2014). A previous study has shown a potential value of combinations of bivariate measures for clinical assessment in a heterogeneous population of comatose patients due to various aetiologies (Zubler et al., 2016). Here we set out to investigate the value of combinations of bivariate quantitative EEG measures as an early prognostic marker in a prospectively collected cohort of comatose patients after CA, postulating that this approach would have a good performance in discriminating patients with good from those with unfavourable prognosis.

2. Materials and methods

2.1. Patients and treatment

This cohort was recruited at the Department of Intensive Care Medicine of the Lausanne University Hospital (CHUV), Switzerland, and is part of a prospective registry containing details of neurological examination (brainstem reflexes, motor reaction, and presence of myoclonus), electroencephalographic features (reactivity, continuity, epileptiform activity), somatosensory evoked potentials, and neuron-specific enolase. For details, please see (Oddo and Rossetti, 2014). The study was approved by the Ethical Committee of the Canton of Vaud. Waiver of consent was granted since the EEGs and clinical information were recorded as part of clinical routine. Consecutive comatose patients admitted in the CHUV Intensive Care Unit from September 2012 to February 2016 after cardiac arrest (CA) and not deceased after 48 h were included. The detailed treatment protocol has been described elsewhere (Oddo and Rossetti, 2014; Rossetti et al., 2010). In short, all patients received TTM, either hypothermia (target temperature 33 °C) or, increasingly since July 2014, controlled normothermia (target temperature 36 °C). TTM was induced as soon as possible using ice packs and ice-cold isotonic solutions, followed by the application of a surface cooling device with automatic temperature control maintained for 24 h. During this time, sedation with midazolam (0.1 mg/kg/h) or propofol (less frequently; 2–3 mg/kg/h), and fentanyl (1.5 μg/kg/h) infusions was provided; vecuronium (0,1 mg/kg), rocuronium (0.6–0.7 mg/kg) or cisatracurium (0.15–0.2 mg/kg) boluses were administered for shivering. Patients with myoclonus and/or electrographic status epilepticus were treated with intravenous seizure suppressive drugs (mainly levetiracetam and valproic acid). The decision to withdraw intensive care support was taken interdisciplinary after at least 72 h, based on the occurrence of at least two of the following criteria: unreactive EEG background after TTM, treatment-resistant myoclonus and/or electrographic status epilepticus, bilateral absence of N20 in somatosensory-evoked potentials after NT/HT, absence from at least one of the three principal brainstem reflexes (pupillary, oculocephalic, and corneal, examined after sedation weaning) (Rossetti et al., 2010). In particular, the EEG during TTM was not taken into account for these decisions.

The neurological outcome at 3 months was prospectively assessed through a semi-structured telephone interview using the Glasgow-Pittsburg Cerebral Performance Categories (CPC) (Booth et al., 2004). Good neurological outcome was defined as CPC 1 (complete recovery) or 2 (moderate disability); poor outcome was defined as CPC 3 (severe disability), 4 (vegetative/unresponsive wakefulness) or 5 (deceased).

2.2. EEG recordings

Video-EEGs (Viasys Neurocare, Madison, WI) recording was performed for 20–30 min during TTM with 19 electrodes according to the international 10:20-system, with reference placed near FpZ. The sampling rate of most EEGs was 250 Hz; three recordings with original sampling rate from 1000 Hz were down-sampled to 250 Hz. From each recording, five minutes (the 30 first 10-s epochs without artifact or patient stimulation, and with closed eyes) were exported for quantitative analysis. Concerning muscular artefacts the following rules were applied: the EEG was excluded if the amplitude of the muscle artefacts after band pass filtering (0.5–20 Hz, see below) exceeded 10% of the averaged peak-to-peak amplitude, as judged by visual analysis. In case of burst-suppression pattern with superimposed muscular artefacts, the EEG was excluded if more than 20% of epochs contained no burst (because of the very low signal-to-noise ratio during suppression epochs). Epoch selection and EEG exclusion were performed prior to quantitative analysis and blind to clinical outcome by two board-certified electroencephalographers (FZ and RK).

2.3. Quantitative EEG analysis

We used four bivariate qEEG measures to characterize the synchronization between the left and right parasagittal (left–right axis, LR), and between the frontal and parietal brain regions (antero-posterior axis, AP) (Zubler et al., 2016). A bipolar derivation was used to represent each brain region: (F3–P3) for the left

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