Clinical Neurophysiology 127 (2016) 2661–2667

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Changes in electrocorticographic beta frequency components precede spreading depolarization in patients with acute brain injury

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ARTICLE INFO

Article history:
Accepted 15 April 2016
Available online 4 May 2016

Keywords:
Spreading depolarization
Ketamine
Beta frequency
EEG

HIGHLIGHTS

- Association between increased SD count and reduced beta frequency was found.
- Ketamine increased relative beta frequency band power and reduced SDs.
- Prospective analysis of beta frequency band alteration might help to predict occurrence of SDs in future studies.

ABSTRACT

Objective: Spreading depolarization (SD) occurs after traumatic brain injury, subarachnoid hemorrhage, malignant hemispheric stroke and intracranial hemorrhage. SD has been associated with secondary brain injury, which can be reduced by ketamine. In this present study frequency bands of electrocorticographic (ECoG) recordings were investigated with regards to SDs.
Methods: A total of 43 patients after acute brain injury were included in this retrospective and explorative study. Relative delta 0.5–4 Hz, theta 4–8 Hz, alpha 8–13 Hz and beta 13–40 Hz bands were analyzed with regards to SD occurrence and analgesic and sedative administration. Higher frequencies, including gamma 40–70 Hz, fast gamma 70–100 Hz and high frequency oscillations 100–200 Hz were analyzed in a subset of patients with a sampling rate of up to 400 Hz.
Results: A close association of relative beta frequency and SD was found. Relative beta frequency was suppressed up to two hours prior to SD when compared to hours with no SD. This finding was partially explained by administration of ketamine. Even after removal of all patient data during administration of ketamine, SDs occurred predominantly during times with low relative beta frequency in a patient-independent analysis.
Conclusion: Suppression of beta frequency by ketamine or without ketamine is associated with low SD counts.
Significance: Alteration of beta frequency might help to predict occurrence of SDs in acutely brain injured patients.

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http://dx.doi.org/10.1016/j.clinph.2016.04.026
1388-2457/

1. Introduction

Spreading depolarization (SD) occurs during the first two weeks after traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), malignant hemispheric stroke (MHS) and intracranial hemorrhage (ICH). In patients with SAH, focal clusters of SDs are observed in brain areas where new ischemia occurs. After SAH and TBI, SDs are associated with DIND (delayed ischemic neurological deficit) and worsened outcome (Dreier et al., 2006; Dreier, 2011; Hartings et al., 2011a,b). In patients with subacute MHS, the incidence of SDs is particularly high (Dohmen et al., 2008). Although SDs are linked to injury of neural tissue and several findings suggest an SD triggered expansion of ischemic zones into previously healthy brain tissue, the nature and extent of SD contribution to secondary brain injury and outcome remains unclear and might be addressed only in treatment studies trying to eliminate or reduce SD occurrence. If a tool would successfully detect SDs prior to first emergence, such treatment studies could be limited to a much smaller number of patients. In previous years on several conferences of the COSBID group (Co-Operative Study on Brain Injury Depolarisations), SD prediction via changes in frequency bands was suggested. The present explorative and retrospective investigation was conducted with the intent to identify changes in the various frequency bands of the electrocorticogram (ECoG) accompanying or even preceding SDs. Analysis was based on hourly means and SDs were attributed to the hour upon detection. How ECoG frequency bands relate to SDs has not been previously studied in patients.

A semiautomated approach was used to analyze digital ECoG. After selection of representative recordings, Fast Fourier Transformation was used to quantify delta, theta, alpha, beta, gamma, fast gamma bands and high frequency oscillations. We related changes in frequency bands to phases before, during and following SD. Since analgesic and sedative drugs have major impact on brain activity and SDs, we controlled for drug related changes in the ECoG frequency bands.

2. Methods

We included a full dataset of 43 patients from three neurointensive care units in our retrospective and explorative analysis (Table 1). Of the 43 patients total, 25 patients had SDs during observation.

All patients had been prospectively enrolled in the Co-Operative Study on Brain Injury Depolarisations (COSBID; www.cosbid.org), a multimodal cerebral observational monitoring study. Patients were not randomized or subject to a treatment study. All procedures were carried out in accordance with the ethical standards laid down in the Declaration of Helsinki and were approved by the research ethics committee responsible for each center.

Patients involved in the study all required craniotomies for ruptured vascular malformations, traumatic brain injury, intracranial hematoma or elevated intracranial pressure subsequent to a massive brain infarct. A subdural strip of six or eight platinum disk electrodes, spaced 10 mm, was placed over the region of interest with the intention to record SDs for the COSBID study (Fig. 1). A reference was placed on the patient's upper torso. Four referenced bipolar ECoG channels were recorded or calculated from eight single channel recordings using Labchart 7 and older versions of this program (ADInstruments, Oxford, UK). All continuous recordings were made in a high noise ICU environment. Recordings during patient care (e.g. patient positioning, physiotherapy) or absence for CT scans were prospectively marked and removed prior to analysis. Visual (manual) artifact rejection was blinded for SD events and only used to reject obvious artifacts such as empty channels with no recordings. Absolute band powers (μV) were extracted using custom written macro routines in Labchart 7 in the following frequency bands according to the international federation of societies for electroencephalography and clinical neurophysiology (www.ifcn.info, Guidelines of the IFCN Chapter 1.5): delta 0.5–4 Hz, theta 4–8 Hz, alpha 8–14 Hz and beta 14–40 Hz. In a second analysis beta1 14–20 Hz, beta2 20–30 Hz and beta3 30–40 Hz sub-bands were analyzed as percentage of beta band. The result of this second analysis is displayed in box plots of Fig. 2(E). Finally, a third analysis for investigation of gamma band 40–70 Hz (Guidelines of the IFCN Chapter 1.5), fast gamma 70–100 Hz and high frequency oscillations 100–200 Hz (Gotman, 2010) was conducted (Fig. 3). All recordings were performed at a sampling rate at or above 200 Hz. Power line interference was eliminated using a notch filter. In 8 patients with recordings at 200 Hz a 50 Hz low pass filter had been applied. This subgroup of patients was therefore excluded from all investigations above beta band. Of the remaining 17 patients, 12 had recordings at 400 Hz with corresponding low pass filter at 200 Hz. For this subgroup of 12 patients high frequency oscillations were analyzed.

All ECoG results are based on hourly mean frequencies of all recorded channels, relative to patient's total power within this hour. Relative band power (%) for delta, theta, alpha and beta frequency was computed per channel by division of power of each frequency band by total power and multiplied by 100. For gamma, fast gamma and high frequency oscillations the same approach was used. The mean frequency of all four channels was further analyzed. After semi automated export from Labchart further data processing was done in Excel. The final database holds hourly measurements in an Excel 2007 spreadsheet (Microsoft Corporation, Redmond, WA, USA).

The database was analyzed using Prism 3.0 (GraphPad Software, San Diego, CA, USA), SPSS 21 (IBM Corporation, Armonk, NY, USA). Individual SDs have a duration of several minutes and fell within the hour of their first detection. We used Bonferroni adjustment for multiple Student's *t*-tests (Table 2A and B). Level of significance for corrected *t*-tests was set to $p < 0.0125$. For column statistics, the median, 25th (lower) and 75th (upper) percentile were tabulated (Fig. 1F). Linear regression and correlation analyses were used to investigate data associations (Fig. 2E). For Fig. 2(A–D), all measured data-points of each patient with SDs ($n = 25$) were used to calculate intraindividual means for band frequencies. For Fig. 2(F) and Table 3 patient means of all patients ($n = 43$) for frequency and anesthetic drug dose was included. A pooled presentation of all measured data-points from patients with no ketamine administration during observation was used for Fig. 2(F). Patient means of all patients with SDs ($n = 25$) was used to calculate Table 2(A). For Table 2(B), patient means ($n = 23$) were calculated from data corresponding to measurements without concomitant administration of ketamine. For two patients no ketamine free interval was available for this analysis. Patient means of gamma and fast gamma bands was analyzed in $n = 17$ patients (Fig. 3A and B). Patient means of high frequency oscillations and how they relate to SD was investigated in $n = 12$ patients (Fig. 3C). Statistical significance was set at $p \leqslant 0.05$.

3. Results

SD is recorded as large potential change with continuous propagation across the cortex (Fig. 1). In patients with electrocorticographic activity in higher frequency bands, SD is accompanied by depression of this brain network activity (Fig. 1, lower four traces).

To investigate how ECoG changed within close proximity to SD an explorative approach was used. Significant differences in mean relative beta frequency power for all investigated hours before and