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Duration of spreading depression is the electrophysiological correlate of infarct growth in malignant hemispheric stroke

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Abstract

Spreading depolarizations (SD) contribute to lesion progression after experimental focal cerebral ischemia while such correlation has never been shown in stroke patients. In this prospective, diagnostic study, we investigate the association of SDs and secondary infarct progression after malignant hemispheric stroke. SDs were continuously monitored for 3–9 days with electrocorticography after decompressive hemicraniectomy for malignant hemispheric stroke. To ensure valid detection and analysis of SDs, a threshold based on the electrocorticographic baseline activity was calculated to identify valid electrocorticographic recordings. Subsequently SD characteristics were analyzed in association to infarct progression based on serial MRI. Overall, 62 patients with a mean stroke volume of $289.6 \pm 68\,cm^3$ were included. Valid electrocorticographic recordings were found in 44/62 patients with a mean recording duration of 139.6 ± 26.5 hours and 52.5 ± 39.5 SDs per patient. Infarct progression of more than 5% was found in 21/44 patients. While the number of SDs was similar between patients with and without infarct progression, the SD-induced depression duration per day was significantly longer in patients with infarct progression (593.8 vs. 314.1 minutes; $^*p = 0.046$). Therefore, infarct progression is associated with a prolonged SD-induced depression duration. Real-time analysis of electrocorticographic recordings may identify secondary stroke progression and help implementing targeted management strategies.

Keywords

Electrocorticography, spreading depolarization, spreading depression, stroke progression, malignant hemispheric stroke

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Introduction

Spreading Depolarization (SD) is the electrophysiological correlate of the initial, still reversible phase of neuronal cytotoxic edema and observed as a large negative direct current (DC)- electrocorticography (ECoG) shift, which spreads between adjacent subdural recording sites. In this context, the SD-induced depression of spontaneous activity is observed as a rapidly evolving reduction in amplitudes in alternating current (AC)-ECoG recordings.[1–3] Recently, DISCHARGE-I, a diagnostic phase III trial in patients suffering aneurysmal subarachnoid hemorrhage (aSAH) has shown that SD-induced depression of ECoG activity – defined as the peak total SD-induced depression duration of a recording day (PTDDD) – reliably indicates impending infarction.[4]

Apart from aSAH,[4–8] SD in humans has also been shown to be associated with secondary ischemic lesion evolution and unfavorable outcome in traumatic brain injury (TBI)[9,10] and intracerebral hemorrhage (ICH).[11] This is highly relevant, because pre-clinical and clinical studies have meanwhile provided evidence that SDs may play an equally critical role for real-time detection of secondary lesion evolution in ischemic stroke: In experimental stroke, infarct progression was proportional to the number of SDs[1,12,13] and the total depolarization time.[14] Moreover, SDs triggered by KCl in the peri-infarct region can propagate into the penumbra and may cause stepwise enlargement of the necrotic core.[15–18] Also, in vivo real-time imaging in lissencephalic and gyrencephalic MCA occlusion models has demonstrated that SDs repeatedly cycle around cortical ischemic lesions and are associated with stepwise lesion enlargement.[19] Interestingly, in humans with malignant hemispheric stroke (MHS) SDs also occur in high incidence[20] with an SD-associated metabolic impairment[21] and inverse neurovascular coupling in the peri-infarct region.[22] These facts and a case-report of a patient with MHS, in which SDs were associated with infarct growth[19] suggests that SDs could also play a critical role in secondary lesion evolution in hemispheric stroke but so far, a direct association between infarct progression and SD could not yet be demonstrated for a larger cohort of patients. SD detection and analysis is hampered in malignant hemispheric stroke by the large size of the primary ischemic lesion as it results in the ECoG electrode more often being placed above infarcted tissue, in which SD cannot occur.[20] Therefore, in the present trial we performed continuous ECoG monitoring and serial MRI in MHS patients and aimed to (i) evaluate a new approach in ECoG analysis that enables identification of valid SD recordings, (ii) analyze the association of SD and secondary infarct progression after malignant hemispheric stroke and (iii) determine the effect of infarct growth on the clinical outcome.

Materials and methods

Standard protocol approvals, registrations, and patient consents

This prospective, multicenter, observational, diagnostic study was approved by the ethics committees of the Charité-Universitätsmedizin Berlin (EA4/109/07, EA4/118/13) and the University Hospital Cologne (AZ: 04-102) in Germany and performed in compliance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act regulations. Patients' informed consent or informed consent from a legally authorized representative was obtained. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (https://www.strobe-statement.org/).

Study design and patient population

Between January 2009 and March 2018, 62 patients with space-occupying middle cerebral artery (MCA) infarction and the clinical need for decompressive hemicraniectomy (DHC) were enrolled in the Co-Operative Study on Brain Injury Depolarization (COSBID). Patients represented in the cohort of the present study may overlap with previously published COSBID projects.[18,21–23]

For the recording of the cortical electrical activity, a subdural, platinum ECoG strip electrode was implanted during surgery and bedside ECoG recording was performed for 3–9 days to determine the association between SD burden and infarct progression. Infarct progression was assessed by serial MRI performed after surgery and at the end of the monitoring period. The initial neurological deficit was assessed using the Glasgow Coma Scale (GCS) and modified National Institutes of Health Stroke Scale (mNIHSS). Outcome at 6 months was assessed using the extended Glasgow Outcome Scale (eGOS). Demographic, clinical and radiographic patient data were analyzed by a clinician who was not directly involved in the patients' care.

Patient management

Treatment was performed according to the guidelines of the German Society of Neurosurgery. Trial inclusion criteria were age $\geq$18 y and subtotal ($\geq$2/3) or total infarction of middle cerebral artery (MCA) territory with or without infarction of the ipsilateral anterior (ACA) or posterior (PCA) cerebral artery

(='Malignant' MCA infarction; MHS) and the clinical need for DHC. The indication for DHC was based on the uniform inclusion criteria of the four randomized controlled trials on hemicraniectomy, DECIMAL, DESTINY I, DESTINY II and HAMLET.[24–26] Trial exclusion criteria were pregnancy, MRI incompatible medical device implants, coagulation abnormalities (thrombocytes < 60 Gpt/l, Quick/PT $< 60\%$, aPTT >45 s), bilaterally fixed and dilated pupils, and/or other evidence of severe, intractable brain injury.

Decompressive hemicraniectomy was performed as described previously.[22,27,28] After bone removal and durotomy, a 6- or 8-contact platinum, subdural ECoG strip electrode (spaced at 10 mm; Wyler, Ad-Tech Medical, Racine, Wisconsin, USA) was placed above the suspected viable, peri-infarct cortical surface area, which was identified by the visible change in tissue appearance at the suspected, cortical infarct border under white light or infrared indocyanine green video-angiography.[29] Postoperatively, patients were transferred to a neurointensive care unit. Intracranial pressure (ICP) was continuously monitored, and patients remained intubated and sedated until ICP was within normal ranges. A critical ICP threshold was defined as ICP > 20 mmHg for longer than 10 minutes and treated with cerebrospinal fluid drainage, osmotic therapy and deep sedation. Blood gases, electrolytes and glucose were controlled every 4 hours. Subdural ECoG recording for SD detection was performed for 3–9 days postoperatively, after which the electrode strip was removed at bedside.

Imaging

According to the study protocol, a first postoperative MRI was performed within 24 hours after surgery to rule out procedure related complications. A second postoperative MRI was performed at the end of the monitoring period after removal of the ECoG electrode. For determination of the infarct volume, brain swelling, and infarct progression between the first and second MRI, matched diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) sequences were used. Infarct volume was corrected for swelling and volumetric analysis was performed using iPlan Cranial surgical planning software (Brainlab AG, Munich, Germany) as reported previously.[23] Additional postoperative CT scans were performed depending on the clinical requirement.

ECoG recording and analysis

Electrocorticographic recording, data processing and analysis were generally performed according to the recommendations of the COSBID research group.[1] Analysis of the recording was done only after discharge of the patients from the ICU, thus the patient's treatment was not influenced by the information obtained from the ECoG recording. The near direct current (DC)/alternating current (AC) ECoG with 0.01–45 Hz bandpass filter was recorded in five bipolar channels at a sampling rate of 200 Hz with a GT205 amplifier (ADInstruments, Dunedin, New Zealand) and Powerlab 16/SP data recording unit (ADInstruments, Dunedin, New Zealand). All nursing activities, such as airway suctioning or patient positioning, were documented in the live data trace with an event marker to facilitate the identification of artifacts.

To ensure valid detection of spreading depolarization, we used a new approach in ECoG analysis. At first, electrocorticographic baseline activity, hereafter referred to as 'baseline power', was analyzed as a correlate of the viability of the tissue and thus its ability to contribute to SD occurrence and spreading, in order to identify patients with correct electrode placement above peri-infarct tissue. Therefore, we determined the mean integral of power of the highpass-filtered activity of all 5 channels (time constant decay, 60 seconds) over 10 minutes in the beginning of the recordings during a recording period without artifacts and outside of the recovery phase after an SD. Later, a cut-off threshold was calculated to identify valid ECoG recordings for further analysis (see 'Statistical Analysis').

Spreading Depolarization was defined by the sequential onset of a propagating, polyphasic slow potential change in adjacent channels, corresponding to the negative slow voltage variation described by Leão.[30] The accompanying ECoG depression was defined by a rapid reduction of power in the highpass-filtered (lower frequency limit 0.5 Hz) ECoG amplitude. When no spontaneous activity was present during the onset of the polyphasic slow potential change in at least one of the channels that showed the slow potential change, SD were classified as isoelectric spreading depolarization (SDi). The duration of the depression period was determined as the interval between depression onset and onset of activity restoration using mathematical integration of the power of the highpass-filtered ECoG activity (time constant delay, 60 seconds).[1,3,10] Spreading Depolarizations were classified as clustered, if an SD occurred within less than one hour after the previous SD had occurred.

Statistical analysis was based on the following SD parameters, according to the COSBID recommendations: number of SDs, number of clustered SDs, peak number of SDs per day (=number of SDs on the day with the maximum number of SDs within a given patient), total SD-induced depression duration of a recording day (TDDD = the sum of the depression

duration of all individual SDs during each 24 h period), peak total SD-induced depression duration of a recording day (PTDDD = longest TDDD among all recording days within a given patient), and total depression duration.[1] To account for individual differences in the recording duration per day, all SD-related variables assessed during the valid recording period within one recording day were normalized to 24 hours of recording duration.[18] Recording days of 24 h were set individually for each patient, starting with the time point of stroke onset, respectively, as defined by the COSBID study group.[1] Thus, day 0 is defined as the first 24 h post-injury, day 1 refers to the following 24 h period and so on. All analyses of the ECoG recordings were performed in LabChart (v8, ADInstruments, New Zealand).

Statistical analysis

Data are presented as median with a range or mean ± standard deviation. All data was tested for normal distribution using the Kolmogorov-Smirnov's test. Correlation analysis for the variables 'initial infarct volume', 'baseline power' and 'SD number' was performed using Spearman's ρ correlation coefficient. Significant correlations were entered into a binary multiple logistic regression analysis after dichotomization of the variable 'baseline power' due to its wide range.

To determine a cut-off threshold for the baseline power that ensures the reliable detection of SD, power threshold levels were calculated according to areas under the curve (AUC) with 95% confidence intervals using receiver operating characteristics (ROC) analysis. Therefore, the baseline power was defined as the binary classifier for the determination of presence ($\geq$1) or absence of SD (including spreading depolarizations and isoelectric SD). Baseline power values above the cut-off were classified as true positive (TP) when SDs were present. Values below the cut-off of the baseline power were classified true negative (TN) when SDs were absent. The test threshold of the baseline power was moved stepwise between 0 and 2500000 μVs.[2] At each step, sensitivity and 1-specificity were calculated. The optimal cutoff threshold for the prediction of SD occurrence was defined as the power value maximizing both the sensitivity and 1-specificity.

Data was dichotomized into patients with no or minor infarct growth (<5%) and into patients with relevant infarct growth ($\geq$5%). Differences of SD parameters between these groups were analyzed by Student's t-test or Mann-Whitney-U-test depending on normality and the sign test for dependent variables. The level of significance was set at $p < 0.05$ and all statistical analysis was performed with SPSS (SPSS for Windows, version 27.0, Chicago, Illinois, USA).

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

Demographics

62 out of 80 consecutively enrolled patients were included in the analysis. Five patients had to be excluded because of insufficient quality of the electrocorticographic (ECoG) recordings, 13 patients had no or only one MRI scan. Briefly, the mean age of all patients was 57 ± 11 years and the mean time from symptom onset to decompression was 39.1 ± 39.3 hours. The mean initial infarct volume after surgery was 289.6 ± 68 cm^3. The mean ECoG recording duration was 137.5 ± 26.9 hours. The mean time interval from surgery to the beginning of the ECoG monitoring was 9.4 ± 6.8 hours. As a maximum of five patients underwent DHC and started being recorded on day 0, defined as the first 24 h after stroke onset, this day is not shown in the figures. No device associated complications occurred. Detailed clinical and demographic characteristics are presented in Supplemental Table 1.

Association between baseline power, SD detection and initial infarct volume

A significant inverse correlation was found between the size of the infarct and the ECoG baseline activity at the beginning of the recording (Spearman's $\rho = -0.321$, *$p = 0.011$, Figure 1(a)). A positive correlation was detected between the baseline activity and the number of detected SDs (Spearman's $\rho = 0.435$, $p < 0.001$, Figure 1(b)). Accordingly, the number of SDs correlated inversely with the initial infarct volume (Spearman's $\rho = -0.287$, $p = 0.024$, Figure 1(c)).

Calculation of the power cut-off threshold for SD detection was performed and the ROC analysis yielded a sufficient classification result (AUC 0.877, 95% CI 0.788–0.966, $p < 0.001$) between 'no SDs' and '$\geq$ 1SD' with a sensitivity of 82% and a specificity of 82% at a power cut-off threshold of 14062 μVs^2 (Figure 1(d)). In 44 patients, baseline power was found to be above the threshold; in 18 patients, baseline power was below the threshold. After dichotomizing patients according to this threshold (dashed line in Figure panels 1(a) and 1(b)), significantly higher infarct volumes (329.4 ± 39.5 vs. 273.3 ± 70.7 cm^3, $p = 0.002$) and less SDs (15 ± 28.1 vs. 52.5 ± 39.5, $p < 0.001$) were noted in the low power group (Supplemental Table 2). Binary multivariable logistic regression confirmed

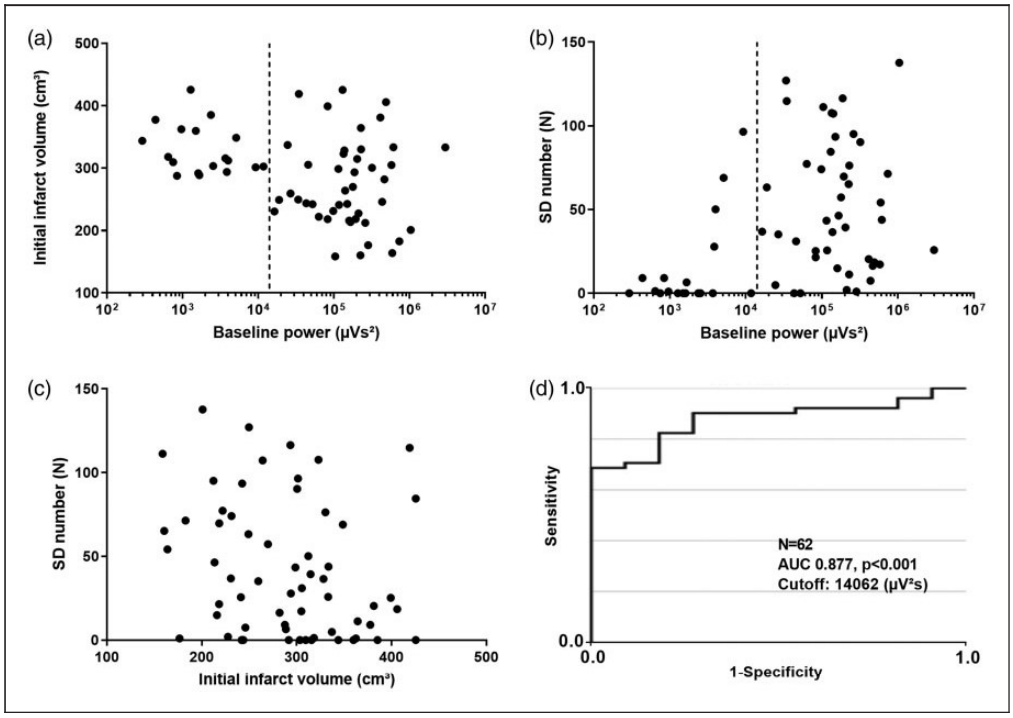

Figure 1. Determination of the power threshold for the detection of SDs in the whole patient cohort (N = 62). Scatter plots of correlation analyses (a–c) display the association of initial infarct volume (corrected for swelling), baseline power (mean of all channels) and SD number (corrected for 24-hour intervals). (d) ROC-Curve of power threshold limit for the detection of ≥1 SD. The test threshold is moved stepwise between 0 and 2500000 μVs^2 of the mean power at start. At each step, sensitivity and 1-specificity are calculated. The power with the combined highest level of sensitivity and specificity was defined as cutoff value.

independent associations between the power above the cut-off threshold and the initial infarct volume (OR 0.986 per cm^3, 95% CI 0.975–0.998, p = 0.02), as well as the SD number (OR 1.035 per SD, 95% CI 1.009–1.061; p = 0.007 (Supplemental Table 2).

The mean recording time in the 44 patients with ECoG baseline power above the threshold was 139.6 ± 26.5 hours per patient (Supplemental Table 1). The total ECoG recording time was 6140 hours, during which 2311 SDs occurred in 42/44 (95%) patients. Out of 2311 SDs, 394 (17%) occurred in electrically inactive tissue (SDi). This yielded a total depression duration per day of 205.2 ± 294.9 min and a PTDDD of 447.6 ± 414.4 min per patient. The number of SDs (Figure 2(a)) and the mean TDDD (Figure 2(b)) were dependent on the recording day with a peak around the first 3 recording days and a decreasing number and mean TDDD thereafter. Detailed results of SD parameters are presented in Supplemental Table 1.

Association between SD and infarct progression

MRI data on infarct progression are presented for all 62 patients (Figure 3(a)) and for the subgroup of 44 patients with ECoG baseline power above the threshold (Figure 3(b)). Overall, the mean time interval from stroke onset to the first MRI was 57 ± 40.8 hours (range 14.8–239.6). The mean time between the first and second MRI was 138.9 ± 27.8 hours. The mean proportion of hemispheric swelling in the first and second MRI was 18.9 ± 8% and 27.7 ± 8%, respectively. Detailed values of MRI analysis are summarized in Supplemental Table 1. 29/62 patients (47%) experienced relevant delayed infarct progression, which we defined as an infarct progression of ≥5% of the corrected infarct volume (Figure 3(a)). A similar proportion was noted in the subgroup of 44 patients with ECoG baseline power above the threshold (Figure 3(b)).

Among the 44 patients with ECoG baseline power above the threshold, no difference was noted between patients with (n = 21) and without (n = 23) relevant infarct progression regarding age, sex, initial infarct volume, NIHSS or GCS. Furthermore, no significant difference was observed between patients with and without infarct progression for the number of SDs per recording day (Figure 4(a)), but the mean TDDD was significantly higher in patients with infarct progression on recording day 2 (p = 0.041) and 3 (p = 0.011, Figure 4(b)). For the whole recording period the mean TDDD and PTDDD were significantly longer in patients with infarct progression (TDDD: 259.0 ± 302.9 min; PTDDD: 593.8 ± 471 min) than in

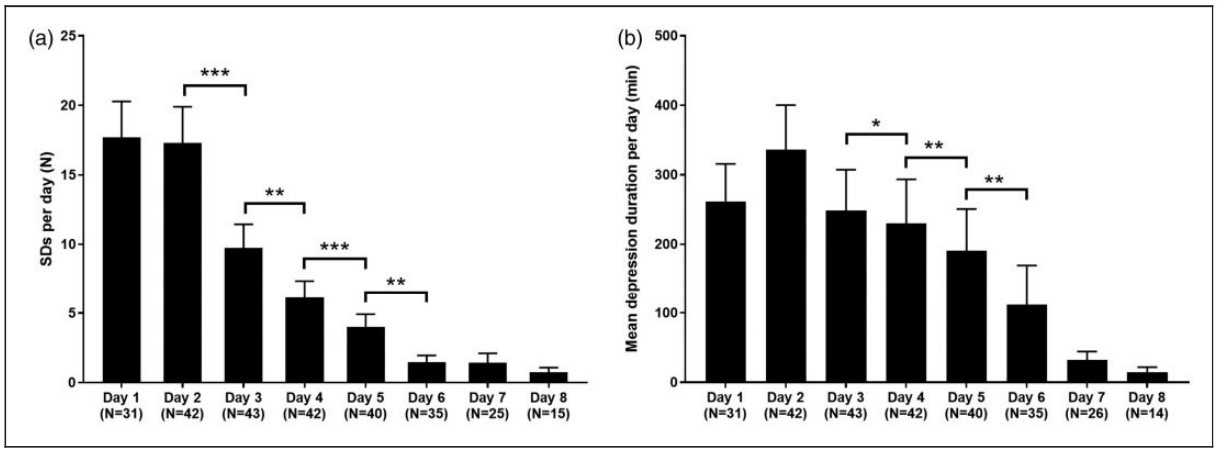

Figure 2. Time course of SD number per day and total SD-induced depression duration of a recording day (TDDD) in cases with ECoG baseline power $>14062\ \mu Vs^2$ (N = 44). (a) Number of SDs per day and (b) TDDD peaked on day 1 and day 2 respectively and decreased significantly (*<0.05) thereafter. Data are displayed as mean of patients and standard error of mean. The number of patients is given in brackets behind the respective day. p-values were determined with the sign test. *N = number, SD = spreading depolarization, TDDD = total SD-induced depression duration of a recording day.*

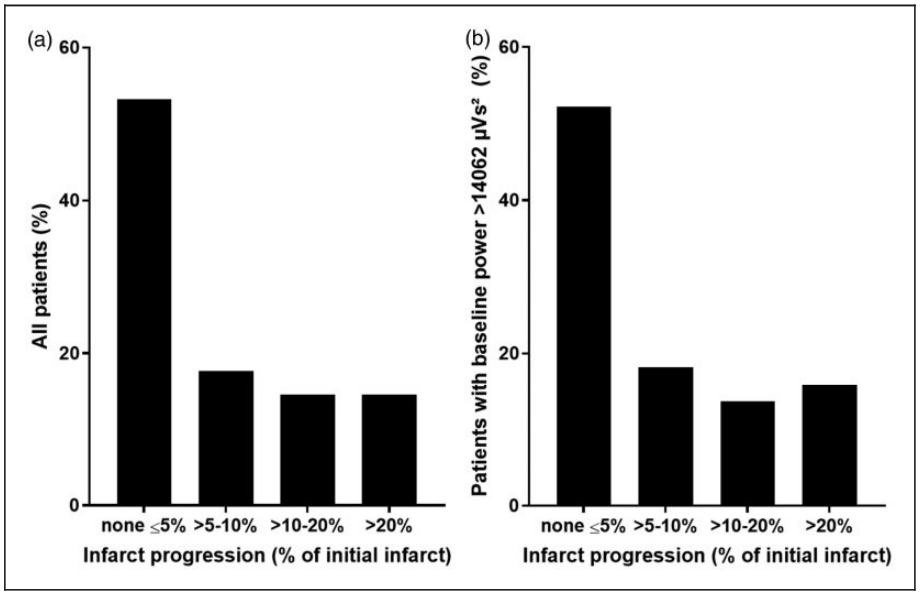

Figure 3. Infarct progression as a function of ECoG baseline power. Infarct progression was determined as percentage of the initial infarct volume among the (a) whole collective of patients (N = 62) and (b) confined to the collective with ECoG baseline power above the threshold (N = 44). The number of patients is displayed as percentage of the respective group.

patients without progression (TDDD: 156 ± 285.2 min, p = 0.046; PTDDD: 314.1 ± 308.2 min, p = 0.046; Supplemental Table 1). An illustrative case of the ECoG monitoring in a patient with infarct progression is shown in Figure 5.

Association between infarct progression and outcome

The extended Glasgow Outcome Scale (eGOS) score at 6 months was available in 45 of all 62 patients. No association was noted between infarct progression and eGOS. In contrast, significant inverse correlations were noted between eGOS at 6 months and the initial infarct volume (Spearman's $\rho = -0{,}434$, p = 0.003), final infarct volume (Spearman's $\rho = -0.412$, p = 0.005), initial GCS (Spearman's $\rho = -0.316$, p = 0.035) and age (Spearman's $\rho = -0.362$, p = 0.014).

Discussion

In this prospective, observational study we show that SD detection via continuous bedside ECoG monitoring

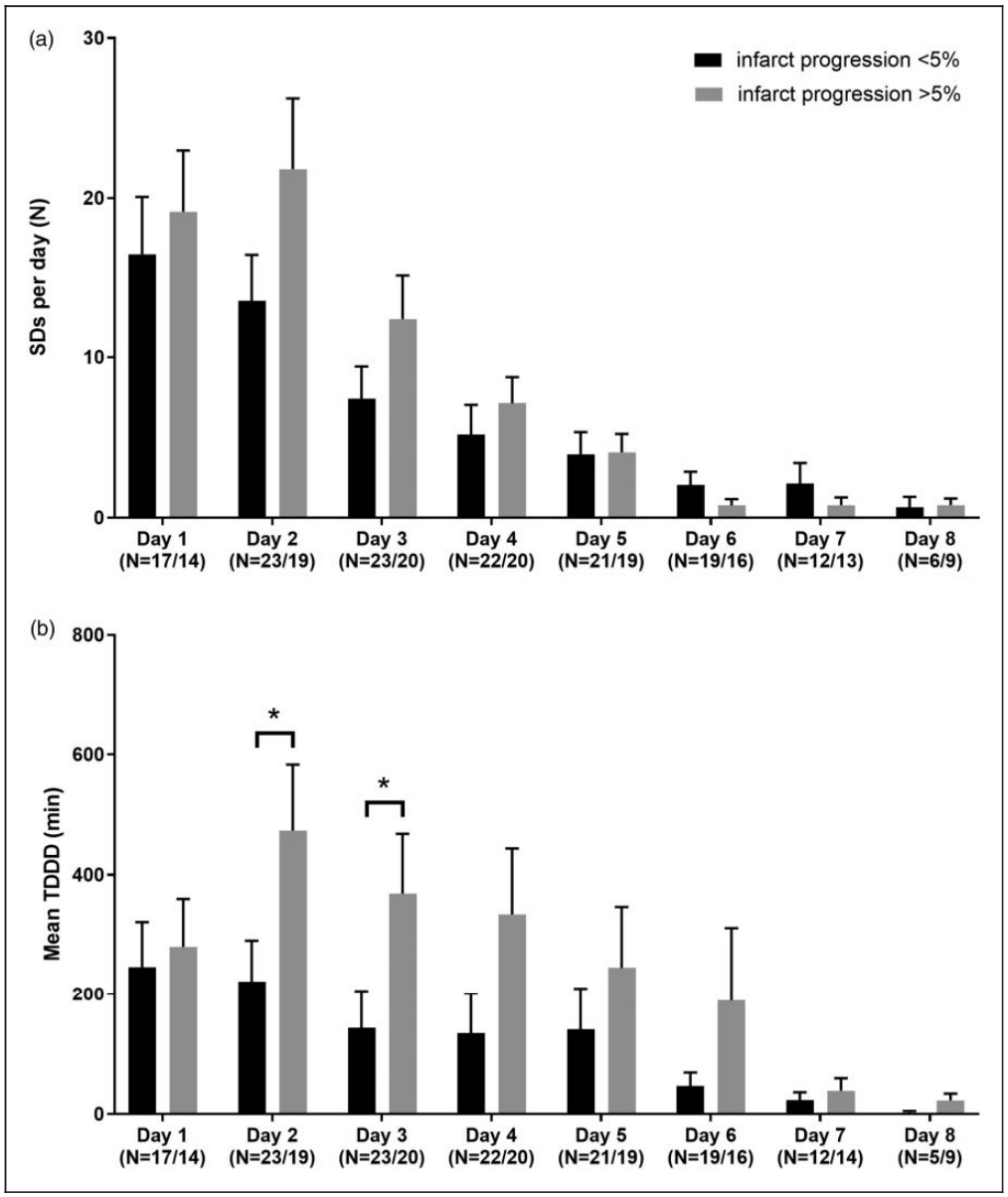

Figure 4. Number of SDs and mean total SD-induced depression duration of a recording day (TDDD) per day. (a) Number of SDs per day and (b) TDDD per day in patients with ECoG baseline power above the threshold (N = 44) dichotomized according to no infarct progression (<5%, black) and infarct progression (>5%, grey). The TDDD in patients with infarct progression was longer on day 2 (*p = 0.041) and 3 (*p = 0.011) after the ictus compared to patients without infarct progression, whereas in the number of SDs no difference was noted. Data are displayed as mean of patients and standard error of mean. The number of patients is given in brackets behind the respective day. p-values were determined with the Mann-Whitney-U-test. *N = number, SD = spreading depolarization, TDDD = total SD-induced depression duration of a recording day.*

in MHS is technically hampered by large infarct sizes. Feasibility of SD monitoring was improved by calculation of an ECoG power cut-off threshold, which allowed us to identify valid SD recordings and ensure reliable SD detection. Using this new approach of ECoG analysis, we were able to show that SD-induced depression duration is associated with infarct progression. These findings underline the relevance of ECoG baseline power assessment for SD recording in cases of widespread cortical injury like hemispheric stroke in order to ensure robust and reliable SD monitoring.

So far, a systematic analysis of the ECoG baseline power has not yet been reported in studies on SD. This is highly relevant, because previous studies on electrocorticographic SD monitoring in MHS reported that in a considerable proportion of patients no SDs occurred.[20] As SD occur regularly and frequently in

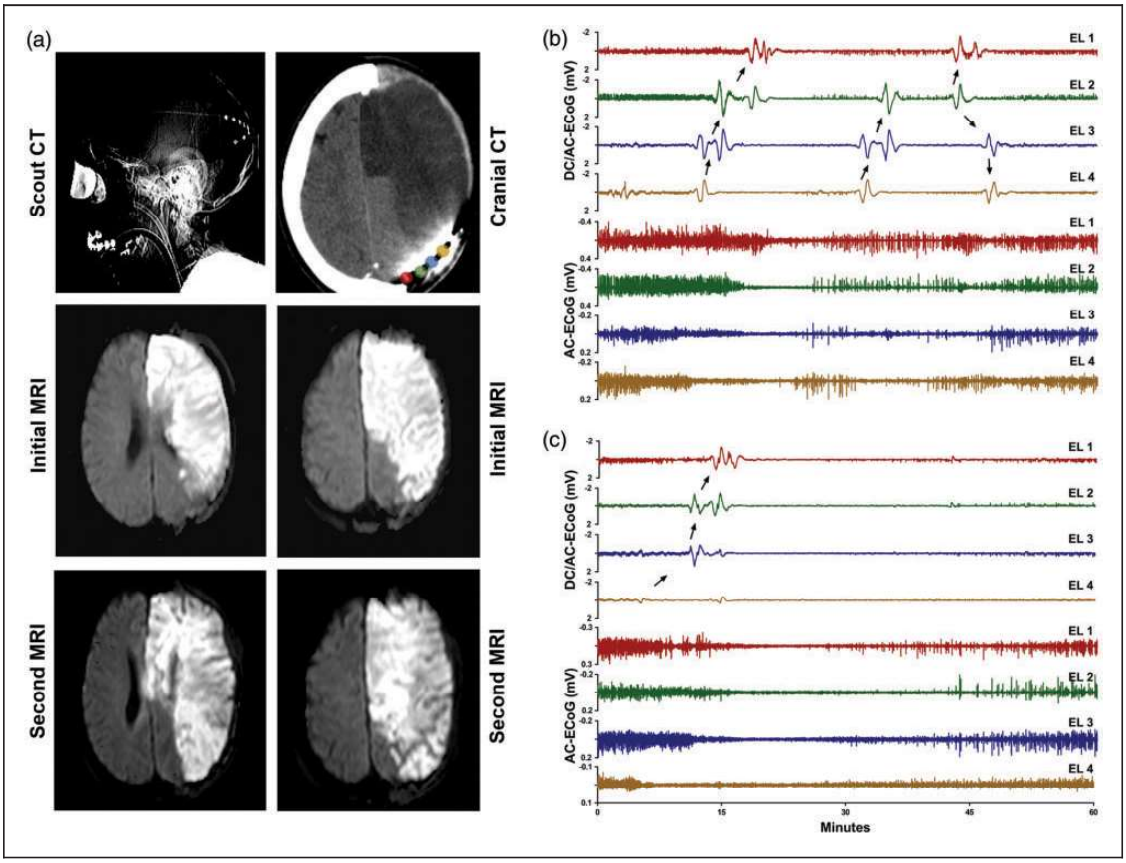

Figure 5. Illustrative Case. (a) Correct positioning of an ECoG strip covering the penumbra and partially the infarct (Scout CT scan, Cranial CT scan). Infarct progression is shown in an initial and second MRI scan at the end of the recording period. The posterior portion of the electrode strip is in the region of secondary lesion progression that developed in the parieto-occipital area between MRI 1 and 2 and had a volume of 24.2 cm^3 (8.3%). ECoG baseline power was confirmed to be 187220 $\mu Vs,^2$ 116.5 SDs were recorded, and peak total depression duration per recording day was 927.2 minutes. (b) Recording of clustered SDs on the first recording day (50 hours post ictus) in near-DC/AC-ECoG recording (bandpass-filtered 0.01–45 Hz). SD induced depression and recovery can be observed in the AC-ECoG (bandpass-filtered 0.5–45 Hz). (c) During disease progression (104 hours post ictus) SDs (DC/AC-ECoG recording) caused prolonged depression durations in the AC-ECoG signal.

hypoperfused brain tissue, the absence of SD rather represents a non-detection due to limitations of the recording method than a non-occurrence of SD. In our cohort the rate of patients with SDs increased to 95% after excluding those with ECoG baseline below the threshold for SD-detection. The same observation has been made by Dohmen et al. who found that after excluding patients where the ECoG strip was placed above infarcted tissue, SD were detected in all patients.[20] To reduce the bias of non-detection, we excluded ECoG recordings with electrodes placed over infarcted tissue by defining a baseline power cut-off threshold that represented sufficient neuronal electrical activity from vital tissue and ensured robust detection of SDs within our patient population. Accordingly, the number of SD correlated with the mean baseline power.

As this is the first study to consider the baseline power of the ECoG recording, it remains unclear if the cut-off value of 14062 μVs^2 calculated in this study, can be used to give recommendations for a general threshold for ECoG analysis. We rather suggest that a power analysis and determination of a cohort-specific cut-off value should be considered when analyzing ECoG data in future studies on SD. Also, we cannot rule out that excluding patients based on a power analysis results in a selection bias with effect on the data reported in the subsequent analyses especially regarding clinical outcome.

After excluding patients with insufficient ECoG recordings, we found that PTDDD but not the number of SDs was significantly higher in patients with relevant infarct progression. This is in line with previous experimental and clinical studies, where the duration of ECoG depression but not the number of SDs was a predictor of experimental infarct growth[14] or delayed infarction after aSAH.[4] This correlation may be explained by extreme deflections of the

physiological equilibrium that accompany the electrical changes and are part of the SD phenomenon. In healthy tissue, SD is naturally accompanied by vasodilatation to support the energy-dependent recovery from SD.[31] In metabolically compromised tissue, such as the peri-infarct region, however, the cerebral blood flow response can be inversely coupled to SD, thereby leading to severe hypoaemia instead of hyperemia and thus a vicious circle of metabolic disturbances.[2,22,32–34] Studies on TBI and MHS described the occurrence of SD to be accompanied by decreased glucose and pyruvate levels and increased levels of glutamate and lactate.[21,23,35] Given this background, the duration of the SD-induced depression of activity is equivalent to the duration of the energy-supply mismatch during SD and thus represents the degree of the metabolic burden. Accordingly, the association of TDDD and infarct progression in this study argues that the occurrence of SDs can be seen as the electrophysiological correlate of infarct progression in hemispheric stroke.

Although the association between initial infarct size, age, GCS and unfavorable outcome in MHS has previously been reported[36] and was confirmed in our cohort, we were unable to detect a significant association between infarct progression and outcome. This may be explained by the fact that the initial infarct volume in MHS patients is already very large which results in a relative secondary lesion growth of only 5%, while it was 44% in a study on aSAH patients with small initial ischemic lesions.[4] Naturally, the large initial lesion size could outweigh the relevance of secondary infarct progression in cases like MHS and accordingly, it seems warranted to discuss whether MHS patients with a generally unfavourable prognosis would at all benefit from SD monitoring and possible interventions. However, possible therapeutic strategies targeting SD such as optimizing physiological variables[18] or initiating sedation with ketamine[37,38] may not only apply to MHS but to all forms of cerebral ischemia and more focal stroke,[19,20,23] since the proportion of potentially salvageable tissue is likely larger in these pathologies. As no device associated complications occurred in this study, we suggest that intraoperative implementation of an ECoG electrode can be seen as a low-risk procedure and as it can meanwhile be performed in a less-invasive fashion without the need for craniotomy,[39,40] it is a clinically feasible method for SD monitoring that also these patients might benefit from. However, the observation time for device associated complications was limited to the time at ICU and long-term monitoring for complications would be needed for a general recommendation to use subdural electrodes for SD monitoring in ischemic stroke patients.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

Christina M. Kowoll: was involved in planning and designing the project, contributed to data analysis of the patients' neuromonitoring, conducted statistical analysis, wrote the manuscript and approved the manuscript before submission.
Leonie Schumm: conducted acquisition of clinical data, performed data analysis of the patients neuromonitoring and imaging, helped writing the manuscript and approved the manuscript before submission.
Alexandra Gieffers: performed data analysis of the patients neuromonitoring and imaging and approved the manuscript before submission.
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Sebastian Major: was involved in the acquisition and analysis of neuromonitoring and clinical data, supervised neuromonitoring techniques in patients, maintained the patients' data base and approved the manuscript before submission.
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Patrick Dömer: was involved in revising the manuscript and approved the manuscript before submission.
Jens P. Dreier: was involved in planning and designing the project, supervised neuromonitoring of the patients, was involved in data acquisition, analysis and interpretation of the neuromonitoring, helped writing the manuscript and approved the manuscript before submission.
Nils Hecht: performed neurosurgical interventions, supervised neuromonitoring of the patients, helped writing the manuscript and approved the manuscript before submission.
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Supplementary material

Supplemental material for this article is available online.

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