BRAIN
ORIGINAL ARTICLE

Reduced brain oxygen response to spreading depolarization predicts worse outcome in ischaemic stroke

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Spreading depolarization (SD) describes a propagating neuronal mass depolarization within the cerebral cortex that represents a mediator of infarct development and strongly stimulates the metabolic rate of O_2 consumption. Here, we investigated the influence of spreading depolarization on brain tissue partial pressure of O_2 ($ptiO_2$) within the peri-infarct tissue of patients suffering malignant hemispheric stroke.

This prospective observational trial included 25 patients with malignant hemispheric stroke that underwent decompressive hemicraniectomy followed by subdural placement of electrodes for electrocorticography (ECoG) and neighbouring implantation of a $ptiO_2$ probe within the peri-infarcted cortex. Continuous side-by-side ECoG + $ptiO_2$ recordings were obtained for 3–6 days postoperatively and analysed for the occurrence of SD-independent and SD-coupled $ptiO_2$ changes, radiological findings, as well as their association with clinical outcome at 6 months.

During the combined ECoG + $ptiO_2$ monitoring period of 2604 h and among 1022 SDs, 483 (47%) SD-coupled $ptiO_2$ variations were identified as biphasic (59%), hypoxic (36%) or hyperoxic (5%) $ptiO_2$ responses that differed significantly ($P < 0.0001$). Among the remaining 538/1022 (53%) SDs, no SD-coupled $ptiO_2$ response was detected, which we categorized as 'No response'. The overall infarct progression was 1.7% (interquartile range −2.5–10.9). SD characteristics regarding type, duration and frequency, as well as SD-independent baseline $ptiO_2$ had no association with outcome. In contrast, a high occurrence rate and amplitude of SD-coupled variations in $ptiO_2$ were associated with improved outcome at 6 months (occurrence: $r = -0.62$, $P = 0.035$; amplitude: $r = -0.57$, $P = 0.024$; Spearman correlation).

In conclusion, an absent or reduced $ptiO_2$ response to SD could indicate tissue-at-risk and help direct targeted treatment strategies in ischaemic stroke, which is further evidence that not all SDs are the same but tissue responses coupled to SD such as $ptiO_2$ contain prognostic information. In particular, a lack of SD-coupled $ptiO_2$ variations appears to be a predictor of worse outcome in large hemispheric stroke.

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Introduction

Spreading depolarization (SD) represents the electrophysiological correlate of the initial, still reversible phase of neuronal cytotoxic oedema and is observed as a large negative direct current (DC)-electrocorticography (ECoG) shift, which spreads between adjacent subdural recording sites. In electrically active tissue, the SD-induced spreading depression is observed as a rapidly evolving reduction in amplitudes of the spontaneous activity in alternating current (AC)-ECoG recordings.[1-3] In peri-infarct tissue, brain activity has usually ceased and SDs that move through this tissue are called isoelectric SDs, as they cannot cause changes in brain activity in the absence of brain activity.[4] In the core region of ischaemia, SDs are characterized by the initial reversible SD component and the transition to the irreversible negative ultraslow potential (NUP),[5] which together form the terminal SD. What all SDs in conditions of brain injury seem to have in common is that they are a real-time biomarker for an increased likelihood of progressive brain damage.[6]

In otherwise normal tissue, SD acts as a strong stimulus to increase regional cerebral blood flow (CBF).[7] However, when the hemodynamic response is severely disturbed, SD can cause severe vasoconstriction instead of vasodilation, resulting in a long-lasting local perfusion deficit (= spreading ischaemia) that prevents tissue repolarization and can eventually even lead to large cortical infarcts.[8,9] When interpreting the response of the brain tissue partial pressure of O_2 ($ptiO_2$) to SD, it should be noted that decreases can be observed even though the CBF response is completely normal, i.e. hyperaemic, as the cerebral metabolic rate of O_2 increases significantly as a result of SD.[10] If this increase is greater than the increase in blood flow, $ptiO_2$ may fall. In animals, even the normal brain, therefore, shows a wide range of $ptiO_2$ responses to SD, ranging from hyperoxic to biphasic hypoxic/hyperoxic to hypoxic.[10,11] Even in the same patient, the full range of these $ptiO_2$ response patterns can occur spatially coupled to SDs that are characterized by adequate neurometabolic coupling.[12] However, it is typical for such $ptiO_2$ responses with adequate neurometabolic coupling that they usually show quite high amplitudes, regardless of whether the $ptiO_2$ change is an increase or a decrease.

From a clinical perspective, this is highly interesting because the cerebral metabolic rate of O_2 is reflected by the degree of brain tissue oxygenation, which can be continuously monitored at the bedside as $ptiO_2$.[13,14] Importantly, $ptiO_2$ is increasingly used to direct haemodynamic therapy,[15-17] and SD can trigger pronounced $ptiO_2$ changes in the clinical and experimental setting.[9,10,18] This suggests that simultaneous assessment of ECoG and $ptiO_2$ may serve as complementary techniques to improve detection and reaction to impending secondary neurological injury,[19,20] but the direct impact of SD-coupled $ptiO_2$ changes on clinical outcome has not yet been determined. Therefore, in the present study, we performed simultaneous side-by-side monitoring of ECoG and $ptiO_2$ in the cortical peri-infarct tissue-at-risk of patients suffering malignant hemispheric stroke (MHS) to determine the effect of SD-coupled $ptiO_2$ responses on clinical outcome.

Materials and methods

Study design and patient population

This prospective observational trial was approved by the ethics committee of the Charité-Universitätsmedizin Berlin, Germany (EA4/109/07, EA4/118/13) and performed in compliance with Health Insurance Portability and Accountability Act regulations. Between January 2009 and December 2017, 25 adult patients with space-occupying middle cerebral artery (MCA) infarction and the clinical need for decompressive hemicraniectomy (DHC) were included after informed consent was obtained. To determine the association between SD-independent and SD-coupled $ptiO_2$ responses and clinical outcome, a subdural, platinum ECoG strip electrode and adjacent, intracortical $ptiO_2$ probe were implanted above the viable peri-infarct tissue at the cortical border of the infarct as determined by intraoperative laser speckle imaging (iLSI) during surgery.[21,22] Bedside ECoG and $ptiO_2$ recording was performed for 3–6 days. To account for individual differences in the recording duration per day, all SD-coupled $ptiO_2$ variables assessed during the valid recording period within one recording day were normalized to 24 h of recording duration.[23]

Infarct progression was assessed by serial MRI 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 modified Rankin Scale (mRS) score. The association between SD characteristics, SD-independent and SD-coupled $ptiO_2$ responses and clinical outcome were determined using a linear mixed effect model and correlation analysis. Demographic, clinical and radiographic patient data and neuromonitoring data were analysed by two separate clinicians not directly involved in the patients' care.

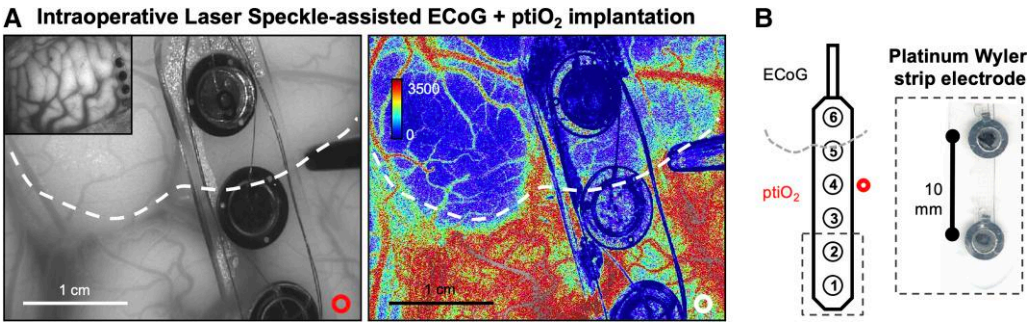

Figure 1 Monitoring setup. (**A**) Intraoperative photo (*left*) and corresponding laser speckle image after opening of the dura and placement of the electrocorticography (ECoG) strip electrode across the cortical infarct border (dashed white line and forceps, *right*) according to the colour-coded cerebral blood flow-flux perfusion map. The red and white open circles indicate the targeted area of polarographic brain tissue O_2 ($ptiO_2$) monitoring probe insertion within the peri-infarct tissue, approximately 10–15 cm from the infarct border. (**B**) Schematic (*left*) and photo image (*right*) of the platinum ECoG strip electrode placed across the infarct border and as close to the $ptiO_2$ probe as technically feasible.

Patient management

Trial inclusion criteria were age ≥18 years and subtotal (≥2/3) or total infarction of 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.[23,24] Trial exclusion criteria were pregnancy, MRI incompatible medical device implants, coagulation abnormalities (thrombocytes <60/nl, Quick value <60%, activated partial thromboplastin time >45 s), bilaterally fixed and dilated pupils, and/or other evidence of severe, intractable brain injury. Decompressive hemicraniectomy was performed as previously described.[26]

After bone removal and durotomy, the cortical infarct border was identified by iLSI (MoorFLPI, Moor Instruments Ltd.) according to an LSI-specific sharp cortical perfusion drop below 40% (LSI recording parameters: frequency: 25 Hz; temporal filter: 100 frames per image; exposure time: 8.4 ms), as previously described.[21,22] To record localized changes in $ptiO_2$ in the peri-infarct tissue, a polarographic brain tissue O_2 monitoring ($ptiO_2$) probe (Licox®, Integra LifeSciences) was inserted subpially within the still viable peri-infarct cortex at a distance of 10–15 mm to the infarct border. To record electrocorticographic activity next to the $ptiO_2$ implantation site, a 6- or 8-contact platinum, subdural ECoG strip electrode (spaced at 10 mm; Wyler, Ad-Tech Medical) was perpendicularly placed across the suspected infarct border, so that the largest proportion of the ECoG recording strip covered the viable peri-infarct tissue and the ECoG electrode was positioned as close to the $ptiO_2$ probe as technically feasible (Fig. 1).[22,25] Postoperatively, patients were transferred to a neurointensive care unit. Intracranial pressure was continuously monitored and patients remained intubated and sedated until the ICP was within normal ranges. A critical ICP threshold was defined as ICP > 20 mmHg for longer than 10 min and treated with CSF drainage, osmotic therapy and deep sedation. Blood gases, electrolytes and glucose were controlled every 4 h. Subdural ECoG and $ptiO_2$ recording was performed for 3–6 days postoperatively, after which the electrode strip and $ptiO_2$ probe were removed at the bedside.

Imaging

A first postoperative MRI was performed within 24 h after surgery and 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. As previously described, infarct volume was corrected for swelling and swelling was determined according to the following method.[26-28] First, we calculated 'volume gain' as 'ipsilateral volume' minus 'contralateral volume'. 'Swelling' was defined as 'volume gain' divided by 'contralateral volume'. Next, the 'volume of infarction corrected for swelling' was calculated as 'volume of infarction'/'swelling + 1'. Volumetric analysis was performed using iPlan Cranial surgical planning software (Brainlab AG).

Recording and analysis of brain tissue partial pressure of O_2 and electrocorticography

Brain tissue oxygen was continuously recorded at a sampling rate of 0.2 Hz with a Powerlab 16/SP data recording unit (ADInstruments). Patients with 'rising' $ptiO_2$ were determined according to an at least 2-fold (= 100%) increase of baseline $ptiO_2$ within the first 48 h. The duration of hypoxic episodes below the $ptiO_2$ baseline thresholds of 15 and 20 mmHg was determined as the total time below threshold and corrected for the different recording durations by normalizing the total time below threshold to the total recording time in each patient. The amplitudes of hypoxic, biphasic or hyperoxic $ptiO_2$ variations were determined as positive differences (delta) between baseline to minimum, minimum to maximum or baseline to maximum, respectively. To determine the association between the proportion of the SD-coupled $ptiO_2$ response types and outcome, patients were grouped according to their 6-month mRS and the normalized number for each of the four different SD-coupled $ptiO_2$ response types was determined for each mRS category. Next, the proportion (occurrence rate) of SD-coupled $ptiO_2$ response types was calculated for each outcome group.

Electrocorticographic recording, data processing and analysis were performed according to the recommendations of the COSBID (Co-Operative Studies on Brain Injury Depolarizations) research group.[1] The near direct current/alternating current (DC/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) and Powerlab 16/SP data recording unit (ADInstruments). SD 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.[29] The accompanying ECoG depression was defined by a rapid reduction of power in the highpass-filtered (lower frequency limit 0.5 Hz) ECoG amplitude. If an SD occurred within less than 1 h after the previous SD had occurred, SDs were classified as clustered (SDc).[1] When no spontaneous activity was present during the onset of the polyphasic slow potential change in at least one channel, isolated or clustered SDs were classified as isoelectric SDs (iSD), which were counted as a single category.

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 artefacts. All analyses of $ptiO_2$ and ECoG recordings were performed in LabChart (v8, ADInstruments).

Statistical analysis

Descriptive summary statistics are reported as mean ± standard deviation, median and interquartile range (IQR) or percentage, as deemed suitable for each variable. The time dependence of $ptiO_2$ values over the observation period was examined using a linear mixed effects model. Fixed covariates included time and time squared. Random effects comprised intercept, time, and time squared. Standard errors and *P*-values are provided for time and time squared. The association between the SD-independent $ptiO_2$ level and outcome was analysed with a two-sided Mann-Whitney U-test. To provide a representative overview of the development of the daily number of SDs and SD-coupled $ptiO_2$ variations, SD numbers and SD-coupled $ptiO_2$ variations were normalized on a per-patient basis according to a 24-h recording period per day and presented as the cumulative daily and overall numbers for all patients. The absolute numbers of SDs and SD-coupled $ptiO_2$ variations are presented in the Supplementary material. Contingency analysis was conducted to examine the various types of SD for each day, the absolute number of SD-coupled ptiO2 responses, the distinct SD-coupled ptiO2 responses observed on each day, and the SD-coupled ptiO2 response corresponding to each SD type, using a chi-square test. The associations between the daily overall number of normalized SD events or SD-coupled $ptiO_2$ responses and the recording time point were assessed using a linear regression analysis. To compare the overall number of different SD types during the valid ECoG and ECoG + $ptiO_2$ recording period and the SD-coupled $ptiO_2$ response patterns, one-way ANOVA with Tukey's multiple comparisons *post hoc* test was used. Associations between SD characteristics and outcome, as well as the SD-coupled $ptiO_2$ responses and outcome, were characterized by Spearman correlation in all patients for whom functional clinical outcome was available at 6 months ($n = 20$). All tests were two-sided and $P < 0.05$ was considered statistically significant. Statistics were performed with GraphPad Prism for Mac (Version 8.4.1, GraphPad Software, San Diego, California, USA) and R (Version 3.5.0, The R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical, demographic and radiographic characteristics

The median age of all patients was 63 (IQR 48–68.5) years. The median time from symptom onset to DHC was 32 (IQR 25–43.5) h. The mean initial infarct volume after surgery was 279 ± 79 ml. The median infarct progression was determined at 1.7% (IQR −2.5–10.9). Of 25 patients, five had no or only one MRI scan and five were lost to mRS follow-up. Detailed patient characteristics are presented in Table 1.

Spreading depolarization-independent brain tissue partial pressure of O_2 response

During the recording period, $ptiO_2$ increased over time, and an initial significant rise in $ptiO_2$ from the beginning of the recording period until approximately Day 4 (time; $P = 0.0005$) was followed by a significant decrease in $ptiO_2$ ($time^2$; $P = 0.0048$) from Day 4 until the end of the recording period on Day 6 (Fig. 2A). However, no difference in outcome was noted between patients with constant (15/25; 60%) versus increasing (10/25; 40%) $ptiO_2$ levels ($P = 0.237$) during the recording period (Fig. 2B). Likewise, there was no association between clinical outcome and the duration of hypoxic episodes during the monitoring period ($ptiO_2 < 15$ mmHg: $P = 0.916$, $ptiO_2 < 20$ mmHg: $P = 0.800$; Supplementary Fig. 1).

Characterization of spreading depolarizations

The recorded absolute number of SDs was normalized to a 24-h recording time per day in each patient. Overall, 1372 SDs were detected during a valid ECoG recording time of 3085 h. During a valid simultaneous ECoG + $ptiO_2$ recording time of 2604 h, 1022 SDs were detected. In both cases, the relative proportions of SD subtypes differed significantly on each day ($P < 0.0001$). Throughout the ECoG and ECoG + $ptiO_2$ recording periods, a significant daily decrease in the number of SDs was noted ($P = 0.001$ for ECoG recording time and $P = 0.003$ for ECoG + $ptiO_2$ recording time) (Fig. 3A). Overall, a significant difference was noted between the three different SD types (SD, SDc and iSD) across the entire ECoG + $ptiO_2$ recording time ($P = 0.044$) (Fig. 3B). The overall SD characteristics regarding type, duration and frequency did not correlate with outcome (Table 2). The individual distribution pattern of the different SD types is presented in Table 3. Absolute SD numbers are presented in Supplementary Fig. 2A and B.

Spreading depolarization-coupled partial pressure of O_2 response

The recorded absolute number of SD-coupled $ptiO_2$ variations were normalized to a 24-h recording time per day in each patient. Overall, an SD-coupled $ptiO_2$ variation was detected in 483/1022 (47%) SDs that were recorded during the combined ECoG + $ptiO_2$ monitoring period. These variations were categorized as hypoxic ($n = 174$), biphasic ($n = 284$) or hyperoxic ($n = 25$) (Fig. 4A). Similar to the subtypes of SD (Fig. 3), their proportion differed significantly on each day ($P < 0.0001$) and a significant daily decrease of the number of SD-coupled $ptiO_2$ variations was noted throughout the ECoG + $ptiO_2$ recording period ($P = 0.011$) (Fig. 4B). For the remaining 539/1022 (53%) SDs, a fourth $ptiO_2$ response pattern was defined as 'No response'. Overall, the occurrence of these 4 $ptiO_2$ response patterns differed significantly ($P = 0.012$) (Fig. 4C), but the proportion of the different $ptiO_2$ response patterns remained unaffected by the underlying SD subtype (Fig. 4D). The individual distribution pattern of the SD-coupled $ptiO_2$ response is presented in Table 3. A corresponding analysis of the 'absolute' number of SD-coupled $ptiO_2$ responses is presented in Supplementary Fig. 2C.

Association between the brain tissue partial pressure of O_2 response and clinical outcome

Next, we looked at the association between the proportion of the SD-coupled $ptiO_2$ response type and clinical outcome and found a significant negative linear association between the occurrence of an SD-coupled $ptiO_2$ variation and outcome, according to the mRS score at 6 months ($R^2 = 0.868$ and $P = 0.021$ for the percentage of

Table I Demographic and clinical patient data

Patient	Initial GCS	Initial mNIHSS	Infarct localization	Time to surgery (h)	Vol. of infarction, cor. (cm^3)	Infarct progression (%)	ECoG/ECoG + $ptiO_2$ (h)	mRS
1	14	11	MCA (R)	14	312	−0.98	105/105	N/A
2	13	13	MCA (R)	22	201	23.8	102/56	6
3	14	12	MCA (R)	43	183	90.4	149/14	3
4	10	16	MCA/ACA (L)	29	301	3.8	90/19	N/A
5	3	N/A	MCA (L)	27	164	0.5	150/148	5
6	12	22	MCA/ACA (R)	32	349	−6.3	164/164	6
7	11	20	MCA (L)	37	260	−9.7	146/146	4
8	13	23	MCA/ACA/PCA (R)	30	364	0.05	140/84	N/A
9	14	14	MCA (R)	46	N/A	N/A	114/114	3
10	3	N/A	MCA (L)	54	159	−13.5	129/104	1
11	3	N/A	MCA/ACA (L)	53	N/A	N/A	152/152	5
12	3	N/A	MCA/ACA (L)	21	N/A	N/A	71/71	6
13	14	12	MCA (R)	44	N/A	N/A	166/166	5
14	14	11	MCA (R)	11	219	4.4	134/134	3
15	3	20	MCA (R)	23	294	−2.5	77/77	6
16	9	28	MCA (R)	29	330	−13.5	97/80	5
17	7	20	MCA/ACA (L)	31	337	11.9	134/134	5
18	3	N/A	MCA (R)	41	243	11.7	83/83	N/A
19	9	20	MCA/ACA (R)	32	426	8.8	176/176	5
20	15	17	MCA (R)	34	161	−0.2	152/129	3
21	7	19	MCA/ACA (R)	22	378	−2.5	139/139	5
22	13	15	MCA (R)	44	250	17.3	133/29	N/A
23	6	19	MCA (R)	46	323	2.9	105/103	6
24	14	13	MCA (R)	36	N/A	N/A	76/76	6
25	3	N/A	MCA/ACA (L)	28	333	4.9	101/101	4
Total	**10 (3–14)**	**17 (13–20)**		**32 (25–43.5)**	**279 ± 79**	**1.7 (−2.5–10.9)**	**123 ± 31/104 ± 45**	**5 (1–6)**

Summary statistics are presented as mean ± standard deviation or median and interquartile range, as appropriate. Bold text indicates descriptive summary statistics. ACA = anterior cerebral artery; cor. = corrected for swelling; ECoG = electrocorticography; GCS = Glasgow Coma Scale score; L = left; MCA = middle cerebral artery; mNIHSS = modified National Institutes of Health Stroke Scale; mRS = modified Rankin Scale score at 6 months; N/A = not available; PCA = posterior cerebral artery; $ptiO_2$ = brain tissue partial pressure of oxygen; R = right; Vol. = volume.

hyperoxic, biphasic and hypoxic $ptiO_2$ responses according to mRS) (Fig. 5A). This was paralleled by a significant negative correlation between functional outcome and the total occurrence rate ($P = 0.035$) as well as the amplitude ($P = 0.024$) of SD-coupled $ptiO_2$ variations (Fig. 5B).

Discussion

In the present study, we show that SD-coupled $ptiO_2$ variations, but not $ptiO_2$ levels alone, can help predict functional outcome in patients suffering large ischaemic stroke. Although the occurrence of SDs was not associated with outcome in the present cohort, the metabolic response to SD was related to outcome in a manner consistent with previous work on neurovascular and metabolic coupling. Specifically, the lack of SD-coupled $ptiO_2$ variations was associated with poor outcome, which could serve as an indicator for metabolically highly impaired tissue and help direct targeted treatment strategies.

In the case of prolonged ischaemia, subsequent SDs originating from the peri-infarct tissue can lead to infarct growth.[6,30] However, not all SDs are equally harmful. Whether SD is locally harmful depends on various factors, such as temperature, baseline level of CBF, neurovascular response and especially the local duration of the respective SD.[31] Overall, almost the full range of SD patterns has now been measured in virtually all major acute brain injuries, including MHS as a prototype of pure ischaemic stroke.[20,32-35] Considering the known implication of SD as the driving force responsible for cytotoxic brain oedema and subsequent ischaemic cell death, bedside SD monitoring is becoming increasingly attractive for obtaining complimentary information regarding the development of secondary neurological injury and brain tissue integrity in patients suffering a severe cerebral insult.[15,16]

Experimentally, SD causes a dramatic increase in the metabolic rate of O_2 consumption, which is paralleled by distinct changes in CBF.[10] Under physiological conditions, the brain can fully recover from the metabolic challenge of re-establishing ion homeostasis during the SD repolarization phase without measurable tissue damage due to a physiological CBF increase as an expression of intact neurovascular coupling.[36] On the other hand, if the extremely high rate of O_2 consumption during SD is not sufficiently met, the SD-associated increase in the metabolic rate of brain tissue O_2 consumption can lead to prolonged tissue hypoxia.[8-10,18] As a result, the extreme O_2 depletion results in prolonged SD duration,[37] prolonged depression of the spontaneous brain activity and lesion progression.[20]

While the technology for recording SD-induced CBF responses is rarely available in patients,[9] $ptiO_2$ represents an established and robust parameter for continuous bedside monitoring of brain tissue oxygenation in neurointensive care. In patients with traumatic brain injury or aneurysmal subarachnoid haemorrhage, decreased brain tissue oxygenation is considered a risk factor for unfavourable outcome[17,38] and critically low $ptiO_2$ levels can also contribute to the elicitation of SDs.[37] Therefore, we first characterized the

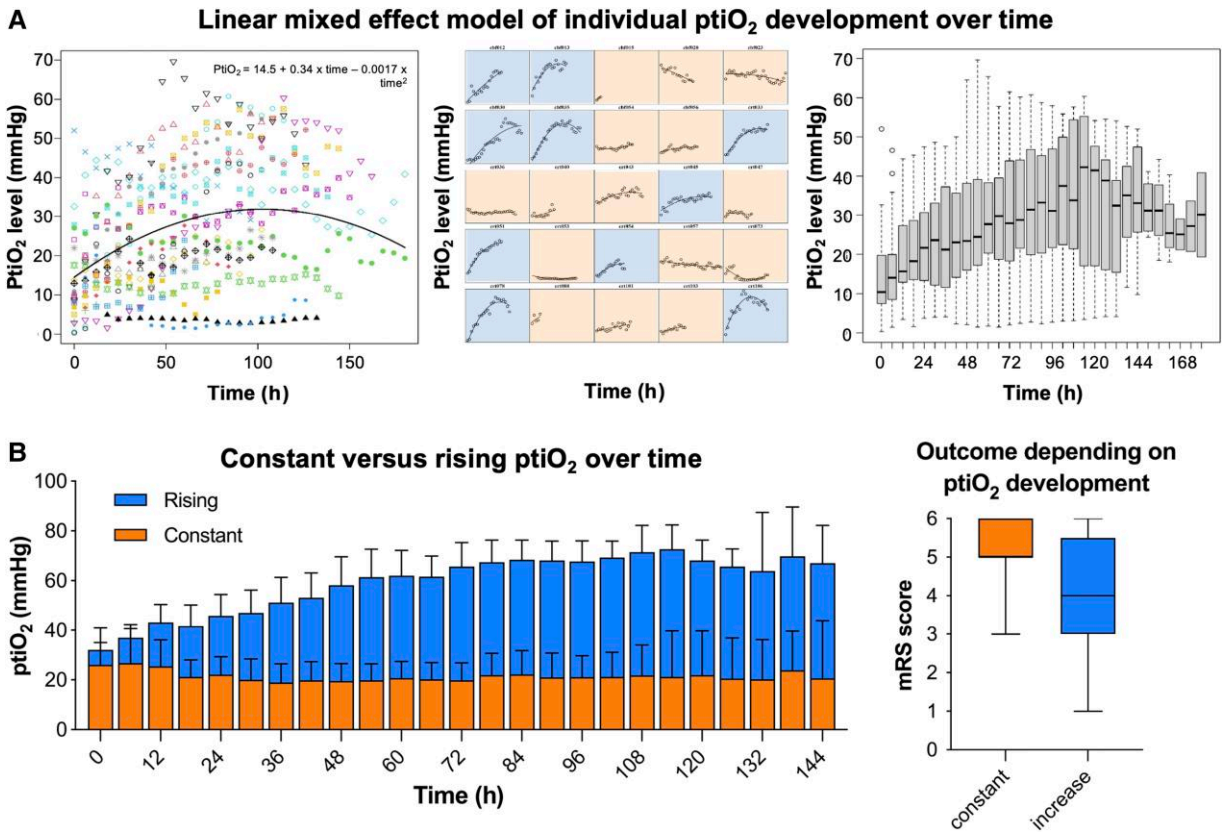

Figure 2 Spreading depolarization-independent brain tissue partial pressure of O_2 response. (**A**) Linear mixed effect model showing the association between the recording time-point and the spreading depolarization (SD)-independent brain tissue partial pressure of O_2 ($ptiO_2$) levels. The mean $ptiO_2$ levels were plotted every 6 h (*left*) and for each patient (*middle*). The blue and orange shading specifies participants categorized as having 'constant' (orange) versus 'rising' (blue) $ptiO_2$ levels during the monitoring period. The definition of 'rising' was based on an at least 2-fold (=100%) increase of baseline $ptiO_2$ within the first 48 h. *Right*: A corresponding box plot with median, interquartile range (box) and range (whiskers). The recording time point had significant effects on the $ptiO_2$ level: First, a significant and nearly linear $ptiO_2$ rise (time; $P = 0.0005$) was noted, followed by a significant decrease in $ptiO_2$ (time^2; $P = 0.0048$). (**B**) Bar graph illustrating SD-independent $ptiO_2$ levels in patients with rising ($n = 10$) versus constant ($n = 15$) $ptiO_2$ until Day 6 (144 h) of the recording period. *Right*: A box plot (median, interquartile range and range) of these groups according to the modified Rankin Scale (mRS) score at 6 months ($P = 0.237$; Mann-Whitney U-test).

pattern of SD-independent $ptiO_2$ levels, where we noted an overall significant $ptiO_2$ increase during the first days of the monitoring period, followed by a gradual decline. Importantly, apart from the first 6 h after $ptiO_2$ probe implantation, median $ptiO_2$ levels generally remained above 15–20 mmHg, which most consider the critical threshold for the development of ischaemic neuronal injury. The gradually rising and then plateauing $ptiO_2$ levels are in part explained by the technical properties of the polarographic $ptiO_2$ probes that we used but could also reflect a consistently improved tissue oxygenation following an improved cerebral perfusion pressure after decompressive surgery or stroke recovery.[28,39] Against this background, a first interesting observation was that hypoxic baseline $ptiO_2$ levels alone were not associated with outcome, which suggests that commonly accepted $ptiO_2$ thresholds in cortical peri-infarct tissue-at-risk might only be of limited prognostic value in large hemispheric stroke.

In a next step, we analysed the number and type of SDs during the ECoG and ECoG + $ptiO_2$ recording time and noted a consistently high proportion of clustered SDs, which impose a higher metabolic demand on the tissue and may be associated with more profound brain injury.[3] The high occurrence rate of clustered SDs also has relevant implications for the development of future treatment strategies because the identification of SD clusters could serve as a threshold to trigger therapeutic interventions aimed at mitigating the harmful effects of SD. The decrease in the daily SD numbers that we noted is at least partially explained by the successive reduction of patients with valid ECoG and ECoG + $ptiO_2$ recording time across the recording period. However, the high extent of the SD reduction beginning around Day 3 indicates that the decrease in the daily SD numbers is most likely not caused by the reduction in patient numbers alone and could also reflect that SD frequency is considered to be highest around the time point of the initial injury.[3,30,40] On the other hand, brain tissue becomes hyperexcitable and more susceptible to SD during cerebral oedema, which progresses during the first week of MHS. In the present cohort, we did not assess oedema but instead determined the total degree of hemispheric swelling because, despite the benefit of DHC in MHS, about 20% of patients still die from herniation due to swelling in the acute phase after hemicraniectomy.[23,24] In our previous analysis of an extended patient cohort that was partially included in the present study, however, the mean proportion of hemispheric swelling remained high even after 1 week (27.7 ± 8% swelling after 1 week versus 18.9 ± 8% swelling in the initial MRI), whereas the occurrence rate of SDs continuously decreased.[41] Together, this argues against a primary association between the degree of swelling and frequency of SD occurrence in MHS. Of course, SDs could also have been triggered by the surgical procedure itself but the overall impact of surgery-induced SDs during DHC is considered negligible.[42] Interestingly, no association was found between

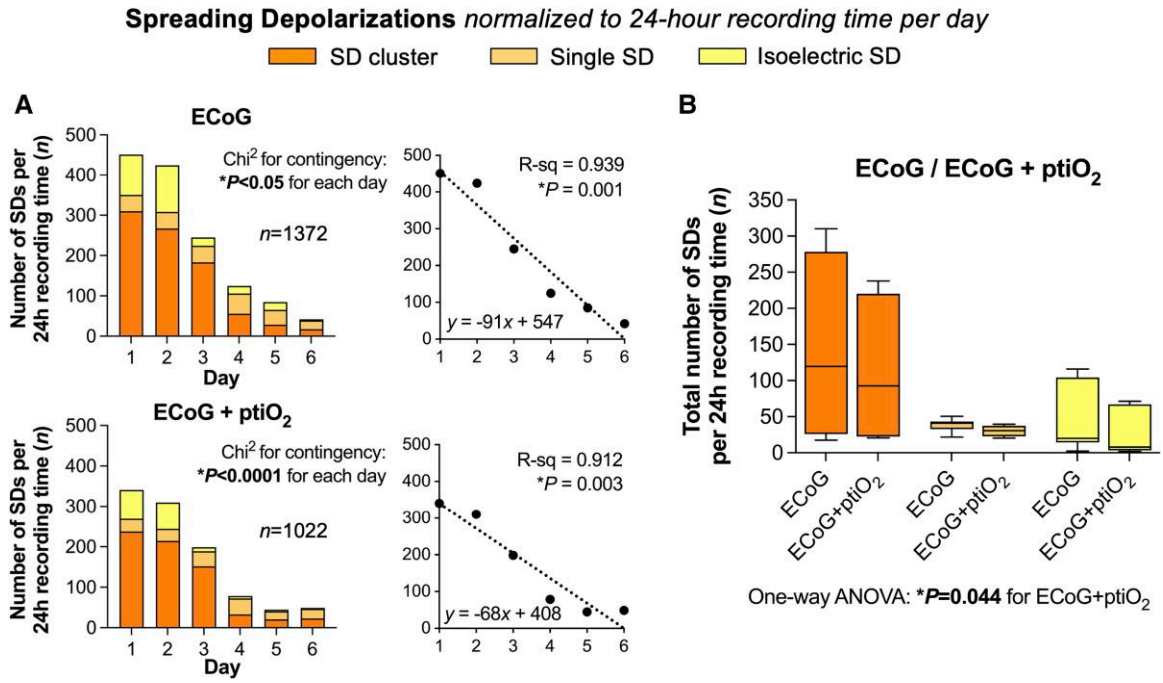

Figure 3 Spreading depolarization characteristics. (**A**) The total number and types of spreading depolarizations (SDs) during the valid electrocorticography (ECoG) (*top*) and ECoG + brain tissue partial pressure of O_2 ($ptiO_2$) (*bottom*) recording is presented for Days 1–6 of the recording period. The daily bar graphs represent the total SD counts of all patients for whom valid recording was available during that 24-h recording period. For the valid ECoG recordings, the number of daily contributing patients was $n = 25$ on Day 1, $n = 25$ on Day 2, $n = 25$ on Day 3, $n = 22$ on Day 4, $n = 18$ on Day 5 and $n = 14$ on Day 6. For the valid ECoG + $ptiO_2$ recordings, the number of daily contributing patients was $n = 25$ on Day 1, $n = 23$ on Day 2, $n = 22$ on Day 3, $n = 21$ on Day 4, $n = 18$ on Day 5 and $n = 14$ on Day 6. The relative proportions of the SD subtypes differed significantly on each day (*P < 0.05 and *P < 0.0001; Chi^2 test). The graphs on the right illustrate the corresponding linear regression analysis of the total number of SDs per day. (**B**) The box plot analysis (median, interquartile range and range) of the total number of SDs during ECoG and ECoG + $ptiO_2$ recordings for each SD-type confirmed a significant difference between the SD subtypes during the combined ECoG + $ptiO_2$ recording time across the entire recording period (one-way ANOVA with Tukey's multiple comparisons test). To account for differences in the individual recording duration, the number of SDs that occurred during the recording time was normalized against a 24-h recording duration per day.

Table 2 Association between spreading depolarization characteristics and clinical outcome at 6 months

SD characteristics correlated to mRS	Spearman ρ (P-value)
Total number of SDs per day/mRS	−0.026 (0.913)
Percentage of SD/mRS	0.245 (0.298)
Number of SDc per day/mRS	0.067 (0.778)
Percentage of SDc/mRS	−0.245 (0.298)
Number of iSD per day/mRS	−0.348 (0.131)
Mean depression time/mRS	0.070 (0.769)
Mean cluster length/mRS	−0.185 (0.478)

Statistics are presented as a measure of strength (Spearmans's ρ) of the association between the spreading depolarization (SD) characteristic and clinical outcome. iSD = isoelectric spreading depolarization; mRS = modified Rankin Scale score at 6 months; SD = single spreading depolarization; SDc = spreading depolarization cluster.

common SD parameters and clinical outcome, which could be at least partially explained by the fact that patients suffered extensive infarct volumes already to begin with, and the overall impact of SDs could have been mitigated by the limited region of SD recording. However, it should be noted that how many SDs may have occurred before or after the recording period is unknown and how this may have affected the association between SD occurrence and outcome.

Third, we characterized SD-associated $ptiO_2$ responses in the viable peri-infarcted cortex next to the ECoG electrode and found that nearly 50% of all SDs of the combined ECoG and $ptiO_2$ monitoring were coupled to a hypoxic, biphasic or hyperoxic $ptiO_2$ variation. Although this is lower than the previously reported 78% SD-coupled $ptiO_2$ variation rate in aneurysmal subarachnoid haemorrhage,[43] an SD-coupled $ptiO_2$ variation appears to be a common and likely relevant pathophysiological variable in cortical tissue undergoing SD propagation. The approximately 50% coupling gap in our cohort may be explained by varying routes of SD propagation in the gyrencephalic brain[34,35,42,44] and differences in spatial resolution between the ECoG and $ptiO_2$ monitoring modalities, for example if separate SDs originated at different sites and propagated into the rather large effective detection area of the ECoG electrode strip but not into the comparatively small (~1 cm^3) detection volume of the $ptiO_2$ probe.[13,14] Also, an unintentional ECoG electrode and/or $ptiO_2$ probe shift during wound closure or patient handling could have contributed to this effect. On the other hand, a pathophysiological reason could be that metabolism in patients 'without' hypoxic, biphasic or hyperoxic $ptiO_2$ variability is no longer sufficiently activated, so that the SD effect on regional $ptiO_2$ is reduced considering that brain tissue oxygenation can mirror downstream cellular O_2 metabolism of the tissue.[10] Therefore, we characterized a missing $ptiO_2$ variability as a fourth distinct $ptiO_2$ response type, since we could not exclude that 'No response' did in fact represent 'intact' $ptiO_2$ coupling recorded in metabolically highly compromised tissue. The second most frequent $ptiO_2$ response that we noted was a biphasic response, followed by hypoxic and very few hyperoxic $ptiO_2$ responses. This frequent occurrence of biphasic $ptiO_2$ responses corresponds to the general concept that biphasic response patterns could mirror a more physiological blood flow response to SD, which, in contrast to a lacking $ptiO_2$

Table 3 Individual distribution of the number of spreading depolarizations and spreading depolarization-coupled brain tissue partial pressure of O_2 responses

	Number of SDs (ECoG recording time)				Number of SD-coupled $ptiO_2$ responses (ECoG + $ptiO_2$ recording time)				
Patient	Total, *n*	SD	SDc	iSD	Total, *n* (%)	No response	Hypoxic	Biphasic	Hyperoxic
1	44	14 (33%)	29 (67%)	0 (0%)	14 (32%)	13 (93%)	0 (0%)	0 (0%)	1 (7%)
2	136	7 (5%)	130 (95%)	0 (0%)	95 (70%)	95 (100%)	0 (0%)	0 (0%)	0 (0%)
3	59	3 (5%)	18 (31%)	38 (64%)	24 (40%)	14 (59%)	5 (23%)	4 (18%)	0 (0%)
4	89	0 (0%)	31 (35%)	58 (65%)	3 (3%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)
5	44	7 (15%)	22 (49%)	16 (36%)	49 (111%)	1 (2%)	15 (31%)	33 (67%)	0 (0%)
6	70	8 (12%)	39 (55%)	23 (33%)	61 (87%)	61 (100%)	0 (0%)	0 (0%)	0 (0%)
7	31	8 (25%)	13 (41%)	11 (34%)	32 (100%)	11 (36%)	4 (13%)	16 (51%)	0 (0%)
8	12	8 (72%)	3 (28%)	0 (0%)	4 (39%)	2 (50%)	2 (50%)	0 (0%)	0 (0%)
9	42	20 (46%)	21 (50%)	1 (3%)	68 (161%)	2 (3%)	23 (34%)	39 (58%)	3 (5%)
10	120	10 (8%)	65 (54%)	45 (38%)	105 (87%)	6 (6%)	13 (12%)	82 (78%)	4 (4%)
11	10	4 (43%)	6 (57%)	0 (0%)	10 (94%)	2 (20%)	6 (64%)	2 (16%)	0 (0%)
12	2	2 (100%)	0 (0%)	0 (0%)	2 (89%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)
13	8	8 (100%)	0 (0%)	0 (0%)	8 (101%)	0 (0%)	2 (24%)	6 (76%)	0 (0%)
14	44	15 (35%)	26 (60%)	2 (5%)	39 (90%)	4 (10%)	0 (0%)	35 (90%)	0 (0%)
15	28	11 (41%)	16 (59%)	0 (0%)	23 (81%)	19 (86%)	1 (4%)	1 (4%)	1 (5%)
16	86	13 (15%)	47 (54%)	26 (31%)	55 (64%)	49 (88%)	2 (4%)	1 (2%)	3 (6%)
17	5	4 (75%)	0 (0%)	1 (25%)	9 (189%)	9 (100%)	0 (0%)	0 (0%)	0 (0%)
18	93	18 (19%)	61 (65%)	14 (15%)	95 (102%)	88 (93%)	1 (1%)	1 (1%)	5 (5%)
19	43	17 (40%)	23 (52%)	3 (7%)	40 (92%)	12 (29%)	20 (50%)	8 (20%)	0 (0%)
20	78	18 (23%)	56 (72%)	4 (6%)	28 (36%)	17 (60%)	6 (22%)	5 (18%)	0 (0%)
21	7	0 (0%)	0 (0%)	7 (100%)	4 (60%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)
22	126	9 (7%)	113 (90%)	4 (3%)	86 (68%)	7 (8%)	34 (40%)	41 (48%)	4 (5%)
23	122	4 (3%)	104 (85%)	14 (12%)	101 (83%)	66 (66%)	26 (25%)	6 (6%)	3 (3%)
24	41	11 (26%)	23 (55%)	8 (18%)	37 (91%)	35 (95%)	2 (5%)	0 (0%)	0 (0%)
25	29	12 (42%)	17 (58%)	0 (0%)	28 (97%)	15 (52%)	10 (37%)	3 (11%)	0 (0%)
Total	**1372**	**231 (17%)**	**863 (63%)**	**277 (20%)**	**1022 (74%)**	**539 (53%)**	**174 (17%)**	**285 (28%)**	**25 (2%)**

To account for differences in the individual recording duration, all data were normalized against a 24-h recording duration per day. Bold text indicates descriptive summary statistics. ECoG = electrocorticography; iSD = isoelectric spreading depolarization; $ptiO_2$ = brain tissue partial pressure of oxygen; SD = spreading depolarization; SDc = spreading depolarization cluster.

response, might reflect a relatively intact metabolic state within the viable peri-infarct tissue.[45,46] Conversely, hypoxic $ptiO_2$ coupling might reflect greater metabolic compromise, but no association was observed between clustered or isoelectric SDs and an increased proportion of hypoxic $ptiO_2$ responses. Another interesting finding was that different SD-coupled $ptiO_2$ responses were recorded in the same location of the same patient, which could be caused by variable haemodynamic response patterns during consecutive SD passages as a result of variable diameter changes in arteries, veins and capillaries in response to SD.[47-49] Another explanation could be an unintentional but still slightly variable cortical insertion depth of the $ptiO_2$ probes between patients, considering the cortical layer-specific magnitude of arteriole dilation following electrical stimulation,[50] layer-specific delivery and consumption of oxygen,[51] and layer-specific oxygenation pattern during 3D SD propagation in the gyrencephalic cortex.[52] Importantly, our present observations underscore the complex interaction between brain parenchyma, the cerebral vasculature and tissue oxygenation during SD.[49,53]

In a last step, we sought to characterize whether SD-coupled $ptiO_2$ response patterns might serve as a prognostic marker for the clinical course of our patients and found a strong relationship between an impairment of the brain oxygen response to SD and worse functional outcome. Conversely, a high frequency (occurrence rate) and also large amplitude of hypoxic, biphasic and hyperoxic SD-coupled $ptiO_2$ variations were associated with better long-term functional outcome at 6 months, which falls in line with the hypothesis that variations of $ptiO_2$ in response to SD represent a more physiological response within viable and metabolically less impaired cortical brain tissue. In other words, if neurons and glial cells are physiologically able to adapt their metabolic rate of O_2 consumption in response to SD, they most likely are under less metabolic stress than neurons and glial cells unable to provide such a response.

As main limitations, we believe that a clear association between a distinct $ptiO_2$ pattern and outcome should be interpreted with caution, considering that the $ptiO_2$ probe localization with regard to the ECoG electrode and the cortical insertion depth could have affected the type of $ptiO_2$ variation that we recorded. Of course, hypoxic metabolic coupling with negative $ptiO_2$ amplitudes could also be interpreted as a sign of infarct progression. However, in our present cohort, infarct progression was merely 1.7%, and different SD subtypes had no effect on the occurrence pattern of SD-coupled $ptiO_2$ responses. Together with the generally reduced occurrence and amplitude of SD-coupled $ptiO_2$ variations that we noted with worsening outcome, we believe that in our cohort the general occurrence and magnitude of a $ptiO_2$ variation, rather than the directionality of its amplitude, indicated whether metabolic coupling to SD was intact. Furthermore, despite no clear signs of technical failure in our analysed dataset, the dilemma remains that we cannot determine with absolute certainty whether the 'No response' type was due to a valid $ptiO_2$ measurement in non-responding tissue or instead caused by an invalid $ptiO_2$ measurement, for example due to technical issues with the oxygen probe or an unintentional and non-detectable probe shift, which might lead to an overestimation of the proportion of SDs with $ptiO_2$ coupling and 'No response'. Lastly, the study was not prospectively powered to test the hypothesis that SD characteristics are related to outcomes.

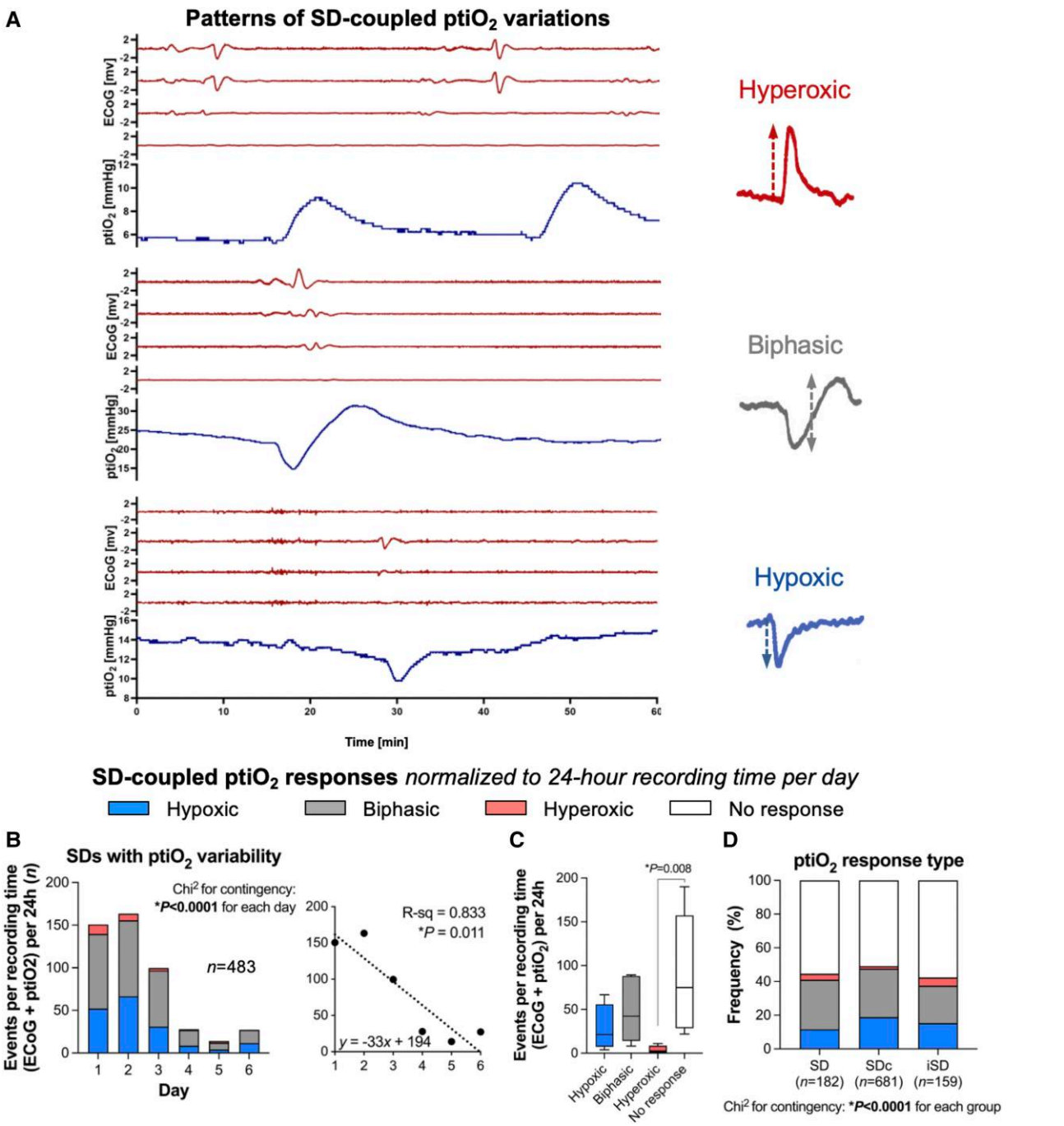

Figure 4 Spreading depolarization-coupled brain tissue partial pressure of O_2 response. (**A**) Live traces (*left*) and schematic (*right*) of corresponding electrocorticography (ECoG) + brain tissue partial pressure of O_2 ($ptiO_2$) recordings displaying representative examples of spreading depolarization (SD)-coupled $ptiO_2$ variations and illustrating the delta of amplitude calculation (arrows). (**B**) The total number and types of SD-coupled $ptiO_2$ variations during the valid ECoG + $ptiO_2$ recording is presented for Days 1–6 of the recording period. The daily bar graphs represent the total counts of SD-coupled $ptiO_2$ variations of all patients for whom valid recording was available during that 24-h recording period. For the valid ECoG + $ptiO_2$ recordings, the number of daily contributing patients was $n = 25$ on Day 1, $n = 23$ on Day 2, $n = 22$ on Day 3, $n = 21$ on Day 4, $n = 18$ on Day 5 and $n = 14$ on Day 6. The relative proportions of the SD-coupled $ptiO_2$ variation subtypes differed significantly on each day ($P < 0.0001$; Chi^2 test). The graph on the right illustrates the corresponding linear regression analysis of the total number of SD-coupled $ptiO_2$ variations per day. (**C**) Box plot analysis (median, interquartile range and range) of the total number of SD-coupled $ptiO_2$ responses, which includes the 'No response' type and shows a significant difference between the four different SD-coupled $ptiO_2$ response types ($P = 0.012$ one-way ANOVA with Tukey's multiple comparisons test) across the entire recording period. (**D**) Frequency distribution of the SD-coupled $ptiO_2$ response types according to the underlying SD ($P < 0.0001$; Chi^2 test) shows a similar distribution pattern of the $ptiO_2$ response types regardless of their underlying SD subtype. SDc = spreading depolarization cluster; iSD = isoelectric spreading depolarization. To account for differences in the individual recording duration, the number of SD-coupled $ptiO_2$ responses was normalized against a 24-h recording duration per day.

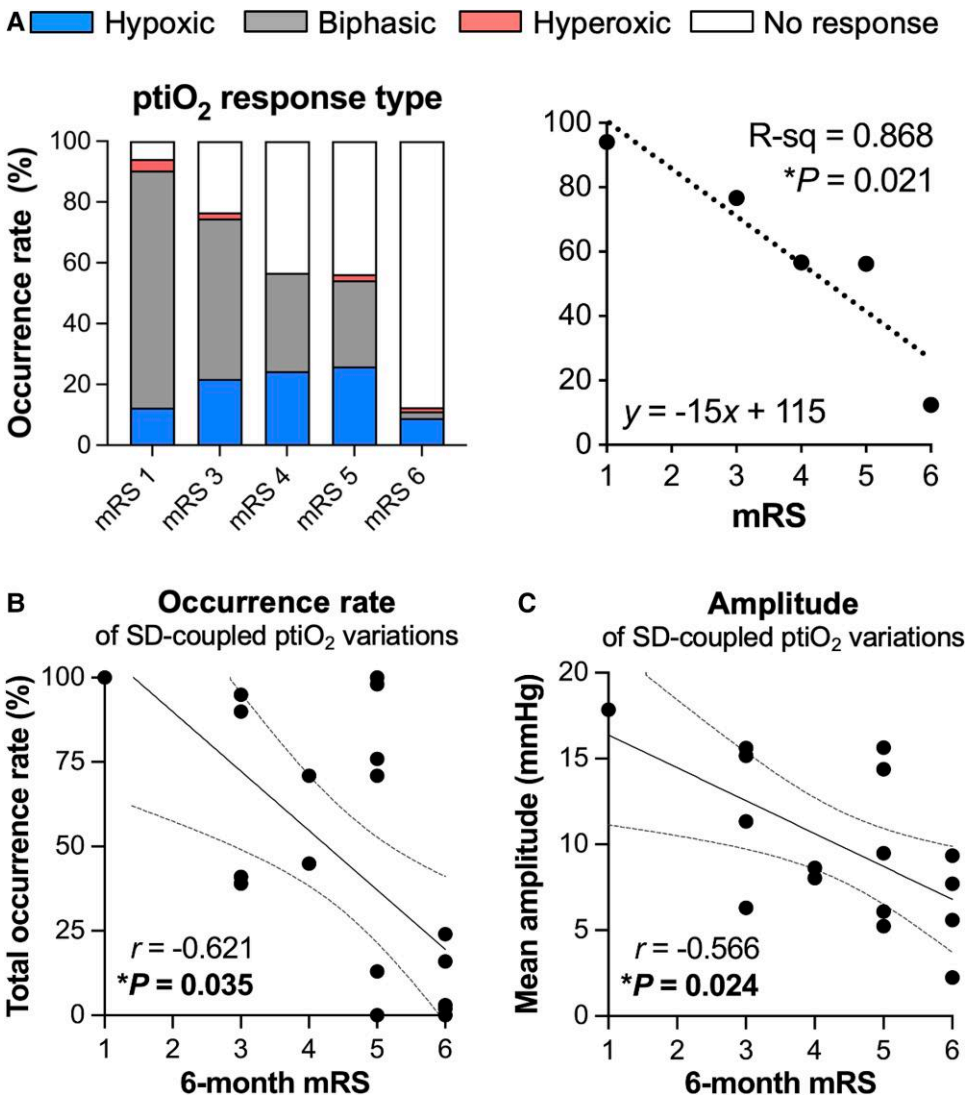

Figure 5 Spreading depolarization-coupled brain tissue partial pressure of O_2 response and outcome. (**A**) Frequency distribution of the spreading depolarization (SD)-coupled brain tissue partial pressure of O_2 ($ptiO_2$) response types according to functional outcome at 6 months. The graph on the *right* illustrates the linear regression analysis corresponding to the occurrence of either one of the three SD-coupled $ptiO_2$ variations (hypoxic, biphasic or hyperoxic). (**B**) Spearman correlation analysis showing the significant association between the occurrence of SD-coupled $ptiO_2$ variations and clinical outcome. (**C**) Spearman correlation analysis showing the significant association between the mean amplitude of SD-coupled $ptiO_2$ variations and clinical outcome. The regression lines and 95% confidence bands are plotted.

Taken together, our findings underscore the relevance of SD-associated $ptiO_2$ response patterns as a possible predictor for patient outcome in large hemispheric stroke. However, the results of this pilot study are limited by the small group of patients, and the findings and clinical relevance necessitate validation in larger cohorts.

Data availability

The analysed datasets may not be shared because the patient's informed consent only permits data analysis and publication by the investigators.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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