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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - EPILEPSY

Screening spreading depolarizations during epilepsy surgery

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Abstract

Background Spreading depolarization (SD) is a fundamental pathophysiological mechanism of both pannecrotic and selective neuronal lesions following deprivation of energy. SD with brain injury has been reported including in one patient during an intracranial operation. However, the incidence of SDs in operative resections is unknown.

Methods We performed (a) retrospective analysis of intraoperative AC-recordings of 69 patients and (b) a prospective study using intraoperative near-DC recording. All patients had the diagnosis of pharmaco-resistant epilepsy. Both studies were designed to determine the incidence and characteristics of SDs intraoperatively. In the retrospective analysis, we used intraoperative electrocorticography (iECoG) recordings obtained from AC-recording of 69 patients. In the prospective analysis, we used an Octal Bio Amp and Power Lab ECoG recorder with near-DC range.

Results In the retrospective study, we included 69 patients with a mean of 1 h 3 min of iECoG recordings. In the prospective study, we recruited 20 patients with near DC recordings. A total of 35 h 41 min of iECoG recordings with mean of 2 h 32 min/patient were analyzed. We did not find SD in either study.

Conclusions SDs were not detected during intraoperative recordings of epilepsy surgery using AC- or DC-amplifiers.

Keywords Spreading depolarization · Epilepsy surgery · Intraoperative recording · Brain injury · Epilepsy

Introduction

Spreading depolarization (SD) describes a phenomenon characterized by the appearance of depolarization waves of neurons and neuroglia that propagate across the gray matter at a speed of 2–9 mm/min [8], with a substantial change in the slow electrical potential for several minutes and a coupled vascular response [8]. The interest in this phenomenon has been growing since the confirmation that it also occurs in humans [28], including subarachnoid hemorrhage (SAH) [7, 19], head trauma [11], stroke [4], and migraine aura [18]. Also, it is associated with epilepsy [10]. SD can produce oxidative stress, worsen hypoxia, and induce neuronal death [5]. For example, in a stroke the core grows (25–50%) as a consequence of spontaneous SDs.

The spectrum of clinical situations where SDs play a role, especially during neurosurgical operations, has not been systematically studied. The possible role of SDs in the intraoperative damage produced during epilepsy surgery is unknown. The use of intraoperative electrocorticographic (iECoG) monitoring during these procedures may provide further insight [21]. A broad band electrocorticography (ECoG) has been suggested to detect SDs [9]. The standard AC intraoperative electrophysiological measurements have physical filters that limit the detection of SDs [3, 9]. Nevertheless, there have been no studies screening the incidence of SDs using intraoperative AC-recordings. In a small study from Carlson et al. [3], ECoG measurements were performed to detect SDs in elective neurosurgeries, including aneurysm clipping, tumor resection, and one arteriovenous malformation. They found two SDs fulfilling all expected characteristics in one patient with a giant pituitary adenoma and eight events that might be SDs in four more patients. The incidence of SDs in neurosurgical

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resections of brain tumors could be indicative of acute progressive damage from mechanical and electrical stimulation. Its incidence may be a prognostic indicator and might explain transient neurological deficits or secondary induced deficits. According to the experimental experience [2], SDs are elicited by minimal neurosurgical stimuli. These events caused transient vasoconstriction and metabolic demand that propagated from the manipulation site. According to Ayata [1], lissencephalic brains are very sensitive to the induction of SDs. SDs can be elicited by mild mechanical or electrical stimulation. In our research group [23–25, 27], SDs in intact swine gyrencephalic brain could not be immediately induced by electrical or mechanical stimulation. SDs could be induced only after preconditioning with high KCl-ringer solution or by occlusion of relevant vessels, such as middle cerebral arteries. How these findings can be translated to the human gyrencephalic brain in the acute phase of brain injury during neurosurgical operations is unknown.

SDs may occur simultaneously with epileptic potentials [8] known as spreading convulsion. This hybrid phenomenon is characterized by epileptic potentials at the end of SD. Not much is known about this phenomenon. The multiple medications used to treat pharmacologic resistant epilepsy may have a positive or negative influence on the appearance of SDs [17, 20].

The main goal of the present study is to discover the incidence of SDs during epilepsy surgery in a retrospective analysis using an AC-ECoG recorder and prospectively using a near-DC ECoG recorder.

Methods and materials

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee Research Committee and Ethics Committee of the National Institute of Neurology and Neurosurgery from Mexico City, Mexico, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Inclusion criteria were as follows: male or female patients aged 18 to 70 years (inclusive) with indication for total or partial resection for focal epilepsy, without previous brain damage. For the retrospective study, formal consent was not required. For the prospective study, a formal consent was obtained from all individual participants included in the study.

Retrospective study

Intraoperative ECoG recordings were implemented with a 64-channel-AC-recorder (EBNeuro S.a.P, Florence, Italy) with Galileo NT software (EBNeuro S.a.P, Florence, Italy, 2008). A mesh of contact electrodes (1 × 8, 6 × 4, 4 × 4, 5 × 4, 6 × 4 contacts) was used according to the requirements of the patient (Integra™ Cedex, France) [21]. During the different phases of the operations, electrodes were placed over the lateral and mesial surfaces of the temporal lobe or in the perilesional surface in extra-temporal surgeries [21].

Indications for surgery were tumors, arteriovenous malformations, mesial temporal sclerosis, alteration of the neuronal architecture, and Lennox-Gastaut syndrome. The kinds of surgery included lesionectomies, extratemporal lobectomies, selective temporal lobectomies, and callosotomies. The characteristics of the patients are included in Table 1. In total, 69 consecutive patients were included in the analysis. The data acquired from the Galileo NT Software was imported in LabChart 7 for analysis. The official criteria for ECoG analysis from COSBID research group for recording, analysis, and interpretation of SD were used [9]. The main variable of interest was the incidence of SDs.

Prospective study

Patients who had indication of elective neurosurgery for the treatment of epilepsy that require iECoG recording were included prospectively in this observational study. Informed consent for monitoring was obtained from all individuals. Exclusion criteria were the interruption of ECoG, recording of less than 30 min, hemodynamic instability resulting in interruption of the operation, and wish of the patient not to continue in the study. The main objective was the detection of SDs. We based the hypothetical SD incidence on previous incidence reported in patients with subarachnoid hemorrhage of 2 SDs/24 h [15]. In 30 patients we would have approximately 60 h of recording. We expected five SDs. A preliminary analysis after 20 patients was planned. After 20 patients, we expected 40 h of monitoring with an incidence of three SDs. If no SDs were found after 20 patients, the study was planned to be stopped.

The secondary objectives of the study were to (a) assess the value of the SD characteristics with regard to its noxious effect, (b) correlate the duration, number and characteristics of SDs, and the induced depression of high-frequency ECoG activity with the size of the resection and other vital parameters studied, and (c) assess the relationship between temporary and permanent neurological deficits and the incidence of SDs.

All patients had a history of intractable seizures and were treated preoperatively with anticonvulsant medication. Minimal doses of sedatives and anxiolytic drugs were administered during the morning of the operation as needed. All operations were performed under general anesthesia.

The iECoG was performed with an 8-contact strip electrode (Ad-Tech, Racine, WI) placed in proximity to the exposed site, approximately 1 cm from the resection site for the closest contact (See Fig. 1). Data were recorded by Octal Bio Amp DC (ADInstruments Brazil) and Powerlab

Table 1 Retrospective study of 69 patient's summary data using AC iECoG recordings

No.	Diagnosis	Presurgical AEDs	Procedure	Time of recording (h/min/s)	Anesthesia maintenance	Grid Localization
31	Left MTE	PHT, CBZ, TPM, LTG, LEV	LTL + AHC	33:40:29	PROP 2340 mg, remifentanyl 2808 mcg, lidocaine 650 mg	T1-T2
34	Right MTE	DZP,VPA,TPM	Glioma resection	37:41:16	Dexmedetomidine 100 mcg, fentanyl 900 mcg, propofol 300 mg	T1-T2
2	Right temporal cavernoma	LEV, VPA	LTL + AHC + cyst exeresis	00:57:05	Desflurane 0.9%—350 ml, fentanyl 1000 mcg, lidocaine 700 mg	T1-T3
1	Right supplementary motor area cystic lesion	PHT	LTL + AHC	00:41:06	Fentanyl 3050 mcg, Propofol 2780 mg	F1-F2
1	Right frontal glioma	LEV, VPA, TPM	Glioma resection	00:24:25	Fentanyl 1286 mcg, Propofol 2570 mg	F1-F2

LTL, left temporal lobectomy; *AHC*, amygdalohippocampectomy; *AEDs*, antiepileptics; *PHT*, phenytoin; *CBZ*, carbamazepine; *TPM*, topiramate; *LTG*, lamotrigine; *LEV*, levetiracetam; *DZP*, diazepam; *VPA*, valproate acid; *PROP*, propofol; *T*, temporal lobe; *F*, frontal lobe; *MTE*, mesial temporal epilepsy

(ADInstruments Brazil) and saved digitally using a LabChart7 (ADInstruments Brazil). A standardized clinical neurological examination and Engel scale were performed 28 days after the operation.

Results

Retrospective study

Sixty-nine patients with a mean of 1 h 3 min 50 s of iECoG recordings were enrolled. Patient details are given in Table 1. The mean age was 32.92 years-old, 31/69 (45%) of patients were women. The diagnoses were the following: right temporal cavernoma (2) cystic lesion in the supplementary motor area (1), right frontal glioma (1), left mesial temporal hippocampal sclerosis (31), and right mesial temporal hippocampal sclerosis (34). The neurosurgical procedures were one callosotomy, 66 were interventions that involved lesionectomies or lobectomies of the temporal lobe and two of the frontal lobes. Fentanyl, propofol, dexmedetomidine, desflurane, and isoflurane were used as maintenance anesthetics. Forty-one patients (60%) had no epileptic seizures or had non-disabling seizures 6 months after surgery (Engel I). We did not find any SD during the iECoG recordings of these neurosurgeries.

Prospective study

We recruited 20 patients with near DC recordings. A total of 35 h 41 min 41 s of iECoG recordings with mean of 2 h 32 min 05 s/patient were analyzed. Patient details are given in Table 2. We found no SD.

Discussion

SD is an electrophysiological concept that was discovered more than 70 years ago by the Brazilian physiologist, Aristides Leão. For almost 55 years, it remained undiscovered in humans [28]. The question of causality together with the non-injurious nature of SD in normal cortex perpetuated skepticism in the past about the relevance of secondary SDs in acute brain injury. Although the precise role of SD in brain

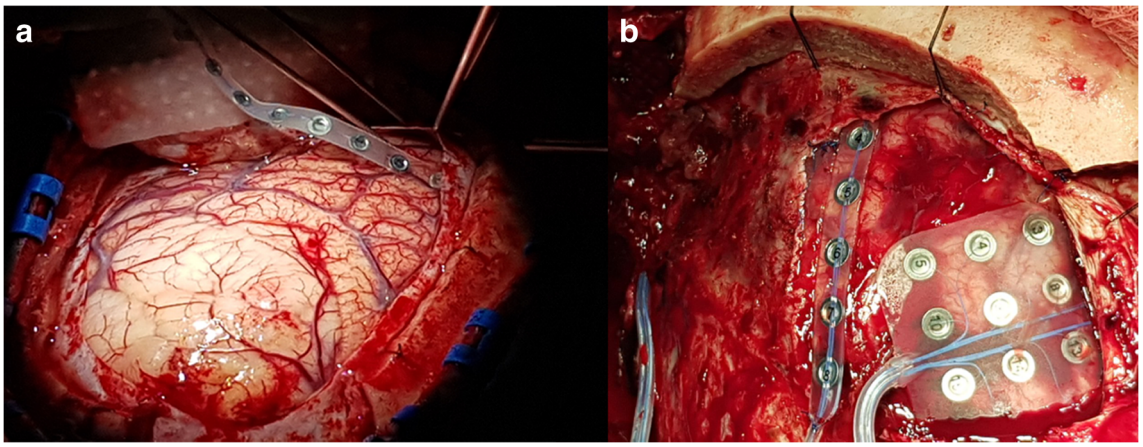

Fig. 1 **a** Placement of 8-contact strip electrode (Ad-Tech, Racine, WI) in proximity to the exposed site, approximately 1 cm from the resection site. **b** Placement of 20 electrodes grid in the site, for electrocorticographic record

Table 2 Prospective study of 20 patient's summary data using DC iECoG recordings

No.	Diagnosis	Presurgical AEDs	Procedure	Time of recording (h/min/s)	Anesthesia maintenance	Grid Localization
1	Right temporal glioma	LEV, VPA	Glioma resection	3:06:26	Fentanyl 2000 mcg, propofol 2 g	T1-T3
1	Right frontal glioma	DZP, VPA, TPM	Glioma resection	0:24:25	Fentanyl 1100 mcg, lidocaine 60 mg, propofol 1930 mg	F2-T1
1	Left temporal glioblastoma multiforme	LEV, VPA	Glioma resection	3:48:23	Desflurane 0.9%—300 ml, fentanyl 1000 mcg, lidocaine 900 mg	T1-T3
1	Left frontotemporal fibrillar astrocytoma	TPM	Glioma resection	2:22:18	Dexmedetomidine 100 mcg, fentanyl 900 mcg, propofol 300 mg	F2-T2
1	Supplementary motor area cystic lesion	VPA	Cyst exeresis	0:41:06	Fentanyl 1800 mcg, lidocaine 1100 mg, propofol 2060 mg, rocuronium 50 mg	F1-F2
1	Left insular astrocytoma	VPA, PHT, LEV	Glioma resection	2:51:56	Fentanyl 1286 mcg, propofol 2570 mg	T1-T3
1	Right neuronal migration disorder	VPA, CBZ	Anterior callosotomy	0:40:55	Lidocaine 100 mg, propofol 2000 mg	F2-T1
4	Left frontotemporal epilepsy	VPA, CBZ, DZP, PHT, LEV, TPM	Anterior callosotomy	5:14:50	Fentanyl 3050 mcg, propofol 2780 mg	F2-T1
1	Left temporal epilepsy	LEV VPA	LATL	2:07:06	Fentanyl 500 mcg, lidocaine 520 mg, propofol 1700 mg	T1-T3
5	Left MTE	PHT, CBZ, TPM, LTG, LEV	LTL + AHC	7:57:47	Propofol 2340 mg, remifentanyl 2808 mcg, xilocaine 650 mg	T1-T3
1	Left glioblastoma multiforme	DZP VPA, TP	Glioma resection	0:55:14	Dexmedetomidine 100 mcg, fentanyl 900 mcg, propofol 300 mg	F2-T2
1	Left temporal epidermoid cystic lesion	LEV, VPA	LTL + AHC + cyst exeresis	3:01:15	Desflurane 0.9%—350 ml, fentanyl 1000 mcg, lidocaine 700 mg,	T1-T3
1	Left epidermoid cystic lesion	PHT	LTL + AHC	2:30:00	Fentanyl 3050 mcg, propofol 2780 mg	T1-T3

LTL, left temporal lobectomy; *AHC*, amygdalohippocampectomy; *LATL*, left anterior temporal lobectomy

damage and repair is not elucidated, several lines of evidence strongly support SD having a causative effect in secondary damage [13].

It is interesting to characterize and screen for SDs in neurosurgical operations, since it could be a good marker of severe acute damage. This could guide intraoperative decision making including administering medication to limit further damage, for example selecting a sedative that could block the SDs [17]. Nevertheless, there are some points that make SD monitoring difficult to achieve in elective operations, namely, artifacts in the ECoG recordings produced by bipolar coagulation, antiepileptic medication of the patients, deep sedation, and short recording windows. Because the ECoG monitoring is a standard in epilepsy surgery, it was for us the practical scenario to screen for SDs first retrospectively using a standard AC-ECoG-recording and later prospectively using an additional near-DC ECoG recorder. This model of near-DC recorder has been used to detect SDs in patients with brain injury by the first author [19, 22].

A second reason that motivated us to screen for SDs during epilepsy surgery was the known associations of SDs with epilepsy [10]. The ictal epileptiform event is the pathophysiological correlate of clinical seizures. The changes during SD are at least five times greater than those seen during epileptiform events [6]. But one important difference between SDs and epileptiform events is that the later are faster, synchronous, and rhythmic. SDs are associated with depression of electrical activity that spread slowly over the cortex forming irregular and heterogeneous patterns [24, 26, 27]. These depressions of activity are easily masked by normal surrounding tissue. SDs cannot be detected using standard scalp EEG. More invasive measurements such as subdural electrodes are required. Experimentally, SD can be detected by the changes produced in molecules, electrolytes, dendritic beading, pH, or free energy among others.

A third reason to screen for SDs in epilepsy surgery is that acute brain damage produces SDs more commonly than epileptic potentials [8]. The estimated incidence of epileptic potentials during the first week after brain damage [9] can be as high as 23% in TBI [29], 38% in aSAH [8], 31% in ICH [30], and 27% in ischemic stroke [16]. SDs in the acute phase was about 56% of patients with TBI [12], 60–70% of patients with ICH [14], 70–80% of patients with aSAH [7], and 100% of patients with malignant hemispheric stroke [4].

To better detect SDs in humans using ECoG monitoring requires an amplifier with DC or near-DC, were used in previous studies [7, 11, 20, 26]. The DC-ECoG recording should be of whole band. This has been certainly a limiting factor why previously no-SDs were detected intraoperatively. This means that the amplifier should not have any filter of slow

frequencies, contrary to what it is standard for recording epileptic potentials or EEG with restricted wavebands. The DC-shifts characteristics of SDs are of very low frequency < 0.05 Hz. These occur as a result of the difference in depolarization between soma and dendrites. After some minutes, those DC shifts can be seen in proximal channels moving with a speed of ~2–9 mm/min. The resultant depression of brain activity can last several minutes, also occurring after some minutes in adjacent channels. Additionally, it is required to filter frequencies above to 45 Hz to eliminate electrical noise. During surgery, it is also important to cancel the artifacts produced by brain mapping and bipolar coagulation.

Despite the three important arguments mentioned above that justify the search for SDs, in our patients we did not find SDs. Therefore, it is worth mentioning that these findings are still relevant since this study is the first that addresses patients undergoing elective epilepsy neurosurgery. Our results have an important translational relevance, since we see a relevant discrepancy between human gyrencephalic brain and rodent lissencephalic brains [2] where SDs appear by minimal mechanical manipulation and coagulation of the brain. One firm conclusion that can be seen from this small study is that under the operative situation of our studied population, the threshold to induce SDs in gyrencephalic human brain is higher than expected, compared with rodent lissencephalic brain.

Reporting of negative results is important to reorient future efforts of the scientific community. Future research will focus on screening for SDs in other scenarios, such as in patients who require temporary clipping of large vessels during aneurysm clipping, patients in awake craniotomies who require brain mapping and are free of sedation, and in patients with large and long operations where brain retraction is required.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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References

1. Ayata C (2013) Pearls and pitfalls in experimental models of spreading depression. Cephalalgia 33(8):604–613
2. Carlson AP, Carter RE, Shuttleworth CW (2012) Vascular, electrophysiological, and metabolic consequences of cortical spreading depression in a mouse model of simulated neurosurgical conditions. Neurol Res 34(3):223–231
3. Carlson AP, William Shuttleworth C, Mead B, Burlbaw B, Krasberg M, Yonas H (2017) Cortical spreading depression occurs during elective neurosurgical procedures. J Neurosurg 126(1):266–273
4. Dohmen C, Sakowitz OW, Fabricius M et al (2008) Spreading depolarizations occur in human ischemic stroke with high incidence. Ann Neurol 63(6):720–728
5. Dreier JP (2011) The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med 17(4):439–447
6. Dreier JP, Reiffurth C (2015) The stroke-migraine depolarization continuum. Neuron 86(4):902–922
7. Dreier JP, Major S, Manning A et al (2009) Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. Brain J Neurol 132(Pt 7:1866–1881
8. Dreier JP, Major S, Pannek H-W et al (2012) Spreading convulsions, spreading depolarization and epileptogenesis in human cerebral cortex. Brain J Neurol 135(Pt 1:259–275
9. Dreier JP, Fabricius M, Ayata C et al (2017) Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: review and recommendations of the COSBID research group. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 37(5):1595–1625
10. Fabricius M, Fuhr S, Willumsen L, Dreier JP, Bhatia R, Boutelle MG, Hartings JA, Bullock R, Strong AJ, Lauritzen M (2008) Association of seizures with cortical spreading depression and peri-infarct depolarisations in the acutely injured human brain. Clin Neurophysiol Off J Int Fed Clin Neurophysiol 119(9):1973–1984
11. Hartings JA, Watanabe T, Bullock MR et al (2011) Spreading depolarizations have prolonged direct current shifts and are associated with poor outcome in brain trauma. Brain J Neurol 134(Pt 5:1529–1540
12. Hartings JA, Wilson JA, Hinzman JM, Pollandt S, Dreier JP, DiNapoli V, Ficker DM, Shutter LA, Andaluz N (2014) Spreading depression in continuous electroencephalography of brain trauma. Ann Neurol 76(5):681–694
13. Hartings JA, Shuttleworth CW, Kirov SA et al (2016) The continuum of spreading depolarizations in acute cortical lesion development: examining Leão's legacy. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. https://doi.org/10.1177/0271678X16654495
14. Helbok R, Schiefecker AJ, Friberg C et al (2017) Spreading depolarizations in patients with spontaneous intracerebral hemorrhage: association with perihematomal edema progression. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 37(5):1871–1882
15. Hertle DN, Dreier JP, Woitzik J et al (2012) Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury. Brain J Neurol 135(Pt 8:2390–2398
16. Jordan KG (2004) Emergency EEG and continuous EEG monitoring in acute ischemic stroke. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc 21(5):341–352
17. Klass A, Sánchez-Porras R, Santos E (2018) Systematic review of the pharmacological agents that have been tested against spreading depolarizations. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 271678X18771440
18. Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ (2011) Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 31(1):17–35
19. Sakowitz OW, Santos E, Nagel A, Krajewski KL, Hertle DN, Vajkoczy P, Dreier JP, Unterberg AW, Sarrafzadeh AS (2013)

Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. Stroke J Cereb Circ 44(1):220–223
20. Sánchez-Porras R, Zheng Z, Sakowitz OW (2015) Pharmacological modulation of spreading depolarizations. Acta Neurochir Suppl 120:153–157
21. San-juan D, Tapia CA, Claudia AT et al (2011) The prognostic role of electrocorticography in tailored temporal lobe surgery. Seizure 20(7):564–569
22. Santos E, Sánchez-Porras R, Dohmen C, Hertle D, Unterberg AW, Sakowitz OW (2012) Spreading depolarizations in a case of migraine-related stroke. Cephalalgia 32(5):433–436
23. Santos E, Schöll M, Sanchez-Porras R, Kentar M, Orakcioglu B, Unterberg A, Dickhaus H, Sakowitz OW (2013) Cortical spreading depression dynamics can be studied using intrinsic optical signal imaging in gyrencephalic animal cortex. Acta Neurochir Suppl 118: 93–97
24. Santos E, Schöll M, Sánchez-Porras R, Dahlem MA, Silos H, Unterberg A, Dickhaus H, Sakowitz OW (2014) Radial, spiral and reverberating waves of spreading depolarization occur in the gyrencephalic brain. NeuroImage 99:244–255
25. Santos E, León F, Silos H, Sanchez-Porras R, Shuttleworth CW, Unterberg A, Sakowitz OW (2016) Incidence, hemodynamic, and electrical characteristics of spreading depolarization in a swine model are affected by local but not by intravenous application of magnesium. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 36(12):2051–2057
26. Santos E, Sánchez-Porras R, Sakowitz OW, Dreier JP, Dahlem MA (2017) Heterogeneous propagation of spreading depolarizations in the lissencephalic and gyrencephalic brain. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab 37(7):2639–2643
27. Schöll MJ, Santos E, Sanchez-Porras R et al (2016) Large field-of-view movement-compensated intrinsic optical signal imaging for the characterization of the haemodynamic response to spreading depolarizations in large gyrencephalic brains. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. https://doi.org/10.1177/0271678X16668988
28. Strong AJ, Fabricius M, Boutelle MG, Hibbins SJ, Hopwood SE, Jones R, Parkin MC, Lauritzen M (2002) Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke J Cereb Circ 33(12):2738–2743
29. Vespa PM, Nenov V, Nuwer MR (1999) Continuous EEG monitoring in the intensive care unit: early findings and clinical efficacy. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc 16(1):1–13
30. Vespa PM, O'Phelan K, Shah M et al (2003) Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. Neurology 60(9):1441–1446