# Propagation of cortical spreading depolarization in the human cortex after malignant stroke

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### ABSTRACT

**Objective:** To investigate hemodynamic response pattern and spatiotemporal propagation of cortical spreading depolarization in the peri-infarct region of malignant hemispheric stroke.

**Methods:** In this prospective observational case study we used intraoperative laser speckle technology to measure cerebral blood flow in patients with malignant hemispheric stroke. Additionally, postoperative occurrence of cortical spreading depolarization was monitored using a subdural recording strip for electrocorticography and infarct progression was assessed by serial MRI.

**Results:** In 7 of 20 patients, 19 blood flow changes typical of cortical spreading depolarizations occurred during a 20-minute period. Thirteen events were characterized by increase, 2 by biphasic response, and 4 by decrease of blood flow. Propagation velocity ranged from 1.7 to 9.2 mm/min and propagation area from 0.1 to 4.8 cm<sup>2</sup>. Intrinsic optical signal alterations preceded and low-frequency vascular fluctuations were suppressed during the hemodynamic responses. A mean number of 56 ± 82 cortical spreading depolarizations per patient was recorded and a mean infarct progression of 30 ± 13 cm<sup>3</sup> was detected in 5 of 7 patients.

**Conclusions:** We visualize the spatiotemporal propagation of spreading depolarizations in the human cerebral cortex intraoperatively. In patients with focal ischemia, multiple cortical spreading depolarizations with either hyperemic or hypoemic flow responses occurred. Our data suggest that, in patients with focal ischemia, cortical spreading depolarizations are associated with both unfavorable and protective hemodynamic responses. *Neurology*<sup>®</sup> **2013;80:1095-1102** 

#### GLOSSARY

**CBF** = cerebral blood flow; **CSD** = cortical spreading depolarization; **ECoG** = electrocorticography; **IOS** = intrinsic optical signal; **LF-VF** = low-frequency vascular fluctuations; **LSI** = laser speckle imaging; **MHS** = malignant hemispheric stroke.

In-hospital lesion progression is a major complication in patients with ischemic stroke. Among numerous pathways for delayed infarct progression, cortical spreading depolarization (CSD) seems very important.<sup>1</sup> CSD describes a wave of neuronal and astroglial mass depolarization.<sup>2</sup> Recovery from CSD is perfusion and energy dependent. In metabolically compromised tissue, progressive damage by CSD is presumably mediated by prolonged mitochondrial depolarization, glutamate release, and neuronal calcium surge.<sup>3</sup> Consistently, in animal models, infarct progression was proportional to the number and summative duration of spontaneous CSDs,<sup>4,5</sup> and artificially triggered CSDs invading the ischemic penumbra recruited further tissue into necrosis.<sup>6–8</sup>

In the clinic, electrophysiologic evidence now exists that CSDs occur abundantly in individuals with malignant hemispheric stroke (MHS).<sup>9</sup> Using electrocorticography (ECoG), CSDs can be measured postoperatively but intraoperative ECoG has largely failed.<sup>10</sup> Laser speckle imaging (LSI) of cerebral blood flow (CBF) can be used alternatively to ECoG for the detection of CSD<sup>11,12</sup> because CSDs entail characteristic changes of CBF.<sup>3,11,13–15</sup> Moreover, CSD causes suppression of low-frequency vascular fluctuations (LF-VF) independent of the hemodynamic response<sup>13</sup> and it is

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associated with intrinsic optical signal (IOS) changes detectable by imaging tools.<sup>16</sup> Here, we intraoperatively used LSI in 20 patients with MHS to screen for CSDs and to monitor their spatiotemporal propagation. We characterized the type of hemodynamic response and investigated the IOS changes. Postoperatively, we recorded CSDs by subdural ECoG, and assessed infarct progression by serial MRI.

**METHODS Standard protocol approvals, registrations, and patient consents.** This study was approved by the local research and ethics committee of the Charité-Universitätsmedizin Berlin. Informed consent was obtained from the patient or legal representative.

**Patient management.** Between May 25, 2009, and February 2, 2011, 33 consecutive patients with subtotal or total middle cerebral artery infarction with or without infarction in the anterior or posterior cerebral artery territory and the clinical need for decompressive hemicraniectomy were screened as eligible for participation in the

current study. Twelve patients were excluded due to unavailability of the monitoring equipment and in one patient study participation was denied by the legal representative. The remaining 20 patients were included in the present study. Treatment was performed according to guidelines of the German Society of Neurosurgery.

For decompressive surgery, all patients were anaesthetized with propofol and remifentanil. During surgery, the mean arterial blood pressure was between 78 and 99 mm Hg (median = 86 mm Hg). After bone removal and durotomy, a laser speckle contrast imager (MoorFLPI, Moor Instruments Ltd., Axminster, UK) was positioned perpendicular over the infarcted hemisphere with a distance of 300 mm as described previously.<sup>17</sup> CBF was recorded within a  $18 \times 24$  cm imaging field with purpose-designed data acquisition software (MoorFLPI measurement software, version V3.0, Moor Instruments, Axminster, UK) at 25 Hz using a temporal filter of 100 frames per image resulting in a scan rate of 0.25 Hz to allow optimal spatial resolution (760  $\times$  568 pixels, exposure time 4 milliseconds). Identical focal lens settings and exposure times were maintained during all measurements. Direct illumination of the surgical field by light sources other than the laser light was avoided. In addition, the backscatter photo image was acquired every 4 seconds (resolution:  $760 \times 568$  pixels). Cortical CBF measurements were performed for 20 minutes. Thereafter, a 6-contact platinum subdural ECoG recording strip (Ad-Tech Medical, Racine, WI) was positioned

Table 1	Summary of intraoperatively recorded CSDs						
Patient no.	CSD no.	Туре	Baseline CBF, units	Velocity, mm/min	Propagation area, cm <sup>2</sup>	Peak, %∆	Plateau, %∆
1	1a	I	906	(7.2)	0.8	46	-
	1b	I	865	(2.7)	0.3	21	-
	2	la	1,113	5.5	1.3	65	_
	3	V	1,716	(8.3)	0.4	-	-58
	4	Ш	1,209	3.8	2.6	97	24
	5	la	738	(5.3)	0.3	52	-
2	6a	Ш	606	(3.6)	0.2	25	-19
	6b	T	660	5.6	1.5	100	-
	6c	II	765	4.6	1.9	117	71
3	7	lp	2,100	4.2	1.3	56	-
	8	lp	1,275	(2.1)	0.2	25	-
	9	$IV^b$	2,026	(1.8)	0.2	-23	-
	10	$IV^b$	1,299	(5.7)	0.1	-13	-
	11	IV	910	(2.3)	0.1	-13	-
4	12	I	1,063	3.8	4.8	26	-
	13	II	779	(6.4)	0.7	83	40
5	14a	V	3,244	(9.2)	0.1	_	-34
	14b	II	1,827	(3.2)	0.2	71	15
	15	I	2,502	(4.1)	0.5	37	-
6	16	II	1,490	3.0	3.6	63	10
	17	Ш	2,098	(6.7)	0.9	24	9
7	18	Ш	815	5.0	1.7	85	24
	19	I	544	1.7	2.0	44	-

Abbreviations: CBF = cerebral blood flow; CSD = cortical spreading depolarization.

<sup>a</sup>Recording stopped before the end of the CSD; therefore, a later plateau could not be excluded.

<sup>b</sup> Recording started after the CSD was already present; the velocity in areas <1 cm<sup>2</sup> was technically difficult to determine and is therefore presented in parentheses.

Figure 1 Time-dependent changes of CBF and IOS in 7 patients with malignant hemispheric stroke



On the left, a schematic drawing is depicted for anatomical orientation (f = frontal, t = temporal, o = occipital). The presented region is marked by a red square. Patient 1 had several spatially dispersed cortical spreading depolarizations (CSDs); therefore, 2 regions are presented (A and B). To the right of the sketch, images of baseline cerebral blood flow (CBF), spread of the hemodynamic response and intrinsic optical signal (IOS) are given. The scale bar marks 10 mm and applies to all frames. Regions outside the cortex are depicted in gray. For characterization of the CSD-associated hemodynamic responses, graph traces from each CSD were analyzed from data that were recorded within the individual regions of interest. CSDs spreading over several gyri were divided into parts (a, b, and c). CSD no. 14 was divided into 2 parts (a and b) because 2 different hemodynamic responses were recognized within the same gyrus.

over the ipsilateral peri-infarct cortex. After surgery, patients were transferred to the intensive care unit. Intracranial pressure was monitored via a pressure sensor (Raumedic, Münchberg, Germany). Blood gases, electrolytes, and glucose were controlled every 4 hours. Sedation with midazolam, propofol, and sufentanil was maintained in patients 1, 4, 5, and 7 for 32, 33, 10, and 38 hours, respectively. In all other patients sedation was immediately withdrawn. MRI was performed after surgery and directly after the monitoring period on day 5–7. Additionally, preoperative MRI scans were performed in individual patients. The initial neurologic deficit was assessed using the Glasgow Coma Scale and modified NIH Stroke Scale. Outcome was evaluated at 6 months using the extended Glasgow Outcome Scale.

Image processing of laser speckle recordings. Image processing of laser speckle recordings is described in the e-Methods on the *Neurology*<sup>®</sup> Web site at www.neurology.org.

**Imaging of the intrinsic optical signal.** Imaging of the intrinsic optical signal is described in the e-Methods.

MRI analysis. MRI analysis is described in the e-Methods.

**ECoG data collection and analysis.** ECoG data collection and analysis are described in the e-Methods.

Statistical analysis. Data are presented as median and range or mean  $\pm$  SD.

**RESULTS** Detailed demographic and clinical data are given in table e-1.

**Propagation of CSD in the peri-infarct tissue.** The mean time from stroke onset to operation was  $26 \pm 10$  hours. In 7 of 20 patients (35%), a total of 19 CSDs were identified with up to 5 CSDs in a single patient (for an example, see video). Two CSDs (CSDs no. 1 and 6) crossed 1 or 2 sulci while all others remained within one gyrus. The CSD area ranged from 0.1 to 4.8 cm<sup>2</sup> with a median size of 0.9 cm<sup>2</sup> per CSD. The median total surface area of all CSDs was 3.7 cm<sup>2</sup> per patient (range 0.8–5.7 cm<sup>2</sup>). The median propagation velocity was 4.2 mm/min with a range from 1.7 to 9.2 mm/min. The detailed velocity and area of each CSD are presented in table 1. The temporal propagation of each CSD over the cerebral cortex during the 20-minute measurement period is illustrated in figure 1.

CSD propagation ended either at a prominent sulcus (for example, see figure 1, CSD no. 6b; video), at ischemic tissue (for clearest example, see figure 1; patient 6), in areas over which a previous hypoemic CSD propagated (figure 1, CSD no. 4 with CSD no. 3 as the previous propagating CSD with hypoemic response), or at major pial vessels (for example, see figure 4). In some cases, no obvious reason was identified.

Hemodynamic response to CSD. A characteristic hemodynamic response pattern in the peri-infarct area after experimental stroke has been consistently reported: the same CSD induced hypoperfusion near the infarct core, whereas it was coupled to hyperperfusion at remote regions.<sup>12,14,18</sup> In our cases, apart from CSD no. 14 all CSDs started and continued with either a

 Neurology 80
 March 19, 2013
 1097

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Figure 2

Spatial (A) and temporal (B) progression of CSDs



With exception of cortical spreading depolarization (CSD) no. 14, we spatially observed only pure hypoemic or hyperemic flow changes. The direction of spread of the hemodynamic change is marked by the arrow and the corresponding time point is presented in mm:ss. The observed flow changes were categorized into 5 types: (I) temporary hyperemia, (II) temporary hyperemia with a subsequent plateau, (III) biphasic response, (IV) temporary hyperefusion, or (V) lasting hypoperfusion. A detailed description of all flow changes is given in table 1. CBF = cerebral blood flow.

monophasic increase or a monophasic decrease of CBF. In CSD no. 14, the hemodynamic response changed from hypoperfusion to hyperperfusion as it spread over the cortex (figure 2).

We observed 5 distinct types of hemodynamic responses: a temporary hyperperfusion with return to baseline (type I), a hyperperfusion with a subsequent positive plateau (type II), a hyperperfusion with a subsequent oligemia (type III), a temporary hypoperfusion with return to baseline (type IV), and a lasting hypoperfusion (type V) (figure 2). Due to our observational time window of 20 minutes, LSI was stopped before CSD nos. 2 and 5 had ended in patient 1. Therefore, in both CSDs we could not exclude a plateau. In contrast, CSD nos. 7-10 were already present at the start of the recording and likewise, a precursory hyperemic or hypoemic CSD could not be excluded. In order to summarize the data, all 19 CSDs are categorized and presented in table 1.

Type I (temporary increase) was observed in 10 gyri undergoing CSDs; the total surface area of a type I response was 13.0 cm<sup>2</sup> in all patients. Type II (increase with subsequent plateau) was observed in 7 gyri and the total surface area accounted for 11.6 cm<sup>2</sup>. A biphasic type III response (increase with subsequent oligemia) was observed just once and accounted for 0.2 cm<sup>2</sup>. Hypoemic flow responses (type IV with a temporary decrease or type V with a lasting decrease) were observed 3 and 2 times and accounted for 0.4 and 0.5 cm<sup>2</sup>, respectively.

The mean positive peak of the hemodynamic response was 58  $\pm$  30% above baseline (100%) and

the positive plateau 28  $\pm$  22%. The negative peak in the hypoemic responses was  $-16 \pm 6\%$  below baseline and the negative plateau  $-37 \pm 20\%$ . Details are given in table 1.

Suppression of LF-VF. Spontaneous LF-VF (frequency range  $\sim$ 0.05–0.1 Hz) are assumed to reflect neural synchrony between brain regions.<sup>13,19</sup> Spreading suppression of LF-VF is one distinct characteristic of CSD13 and was observed in CSD no. 6b of patient 2 of our study (figure 3). During CSD, the mean power of the amplitude changed from  $109 \pm 58\%$ to  $12 \pm 4\%$ .<sup>2</sup>

Changes in pial vessel diameter associated with CSD. Only in patient 3, pial vessel diameter changes were associated with a hemodynamic response to CSD. Figure 4 depicts two pial arteries with significant dilation during local hyperperfusion. The vessels dilated from 0.46  $\pm$  0.05 mm to 0.84  $\pm$  0.03 mm  $(83 \pm 25\%).$ 

Intrinsic optical signal. Mapping of the cortical IOS can be used experimentally to study the spatiotemporal propagation of CSDs in high resolution.<sup>16</sup> In this clinical study, the IOS change represented a narrow band running at the wave front of the CSD (see video). Figure 1 shows the spread of the IOS change. The IOS change in patients 2 and 7 was characterized by an increase in brightness, whereas the IOS in patients 3, 4, and 6 was characterized by a decrease in brightness. Not every CSD was associated with a detectable IOS change.



(A) Spatial distribution of the alternating flow changes at different time points with superimposed regions of interest (ROIs) for further analysis. (B, C) Cerebral blood flow (CBF) changes in ROI 1 and 2. The arrow marks the spread of the area with CBF changes between the ROIs. (D, E) The bandpass filtered (0.05-0.1 Hz) CBF signal demonstrates the spread of the suppression of low-frequency vascular fluctuations (LF-VF).

Postoperative monitoring and infarct progression. The mean time interval from surgery to the start of ECoG monitoring was  $5.5 \pm 3.7$  hours. The median monitoring period was 149 hours per patient (range 122–164 hours). In 2 of our 7 patients, no CSD was recorded during the postoperative period. In the remaining 5 patients, 391 CSDs were recorded, with a mean number of 78 ± 88 CSDs per patient. Nineteen CSDs occurred while there was no background activity (isoelectric CSDs). The total summative time of ECoG depression was 3,797 minutes (mean time 759 ± 541 minutes per patient). The mean stroke volume determined by the MRI directly after surgery was 281 ± 68 cm<sup>3</sup>. Patients 5 and 6 had no infarct progression while the remaining 5 patients had a median infarct progression of 28 cm<sup>3</sup>

(range 12–48 cm<sup>3</sup>). Detailed postoperative monitoring data are presented in table e-1.

**DISCUSSION** CSDs can be characterized and detected by their distinct changes of electrical gradients, pH and ion shifts, efflux of amino acids, changes in CBF, oxygenation, and IOS.<sup>2,11–14,16,20–22</sup> Against this background, LSI allows the measurement of the hemodynamic responses with high spatiotemporal resolution and constitutes an ideal tool in order to study the propagation of CSDs. The first experimental setup to assess CSDs by LSI was described in 2001.<sup>23</sup> Since then, this technology has significantly contributed to a better understanding of the impact of CSDs on progressive tissue damage after experimental ischemia.<sup>11,12,14,18,24</sup>

Leão25 discovered in 1944 that transient vasodilatation is coupled to CSD in healthy tissue. This vasodilative/ hyperemic response serves the energy-dependent recovery from CSD because it increases delivery of energy substrates and tissue clearance.26 Despite this hyperemic response, transient tissue hypoxia can be found in most distant supply territories of cortical capillaries.<sup>27</sup> Under such physiologic conditions, CSD is followed by oligemia,28 during which vascular responses to changes in the arterial partial pressure of CO2 and functional activation are transiently attenuated.<sup>29</sup> In the ischemic penumbra, however, this preexisting vascular disturbance hampers sufficient oxygen and glucose supply.<sup>30-32</sup> Moreover, CBF may be inversely coupled to CSD, leading to severe hypoemia instead of hyperemia.3,11-14,33

Experimentally, LSI evidenced that depending on the distance to the infarct core, the same CSD can be associated with a monophasic hypoperfusion (at a distance near to the core), a biphasic hypoperfusion and hyperperfusion (at an intermediate distance), or a monophasic hyperemia (in the periphery of the ischemia).<sup>12,14,18</sup> In addition to such a radial spread, CSDs were found to orbit the infarct core, recruiting more and more tissue into severe hypoperfusion.11,12,24 In the present study, we observed multiple CSDs with either hyperperfusion or hypoperfusion. The latter, in particular, was restricted to only small cortical areas. Neither a wide radial spread nor a circling around the ischemic core was observed in the present study. This local restriction of CSDs that was not seen in experimental studies could be due to species differences. But it could also be explained, at least partially, by the delayed and limited observation period in our study (12-43 hours after stroke onset) and the fact that only part of the cortical tissue was exposed at the brain surface, while the rest was hidden in sulci and fissures. On the other hand, this local restriction of the CSDs is clinically interesting because it could explain why ischemic stroke is not usually associated with a status aurae migraenalis, a state with recurrent migraine auras<sup>34</sup>: if

Figure 4 Change of pial vessel diameter associated with flow alterations in patient 3



(A) Photograph of the cortex and pial vessels with superimposed spreading area of altered blood flow at 1 minute. (B) Same area at 20 minutes with superimposed dashed rectangles that illustrate 2 subsequently magnified regions; at 20 minutes no blood flow alterations were visible. The bottom magnified region at 1 minute (C) and 20 minutes (D) shows a significantly larger pial artery (red arrow) at the time point with flow increase. (E, F) Upper magnified region shows a second significantly larger pial artery at the time point of flow increase. The scale bar marks 15 or 5 mm and applies to panels A and B or to panels C to F, respectively.

recurrent CSDs propagated over large brain regions, patients with ischemic stroke in the territory of the middle cerebral artery should experience a visual status aurae migraenalis because the CSDs would trigger recurrent spreading depressions of spontaneous activity in the visual cortex.<sup>20,34</sup> The present data suggest that such a status aurae migraenalis is so rare in ischemic stroke<sup>34</sup> because intrinsic mechanisms usually limit the propagation of peri-infarct CSDs into remote, functional tissue. For more comprehensive accounts of the different depression patterns associated with CSD in healthy and ischemic tissue, we refer the reader to 2 previous reviews.<sup>3,21</sup>

In the present study, we saw a median infarct progression of 28 cm<sup>3</sup> in 5 of 7 patients. However, in this small patient population, it was not possible to determine a correlation between infarct progression and frequency of intraoperative CSDs and combined intraoperative and postoperative CSDs, respectively.

In the video, we superimposed the infarct border from 3D reconstructions of a directly preoperative MRI. It is evident that the CSD propagates over areas with already infarcted tissue as defined by diffusionweighted imaging and fluid-attenuated inversion recovery pulse sequences. Although there is no histologic proof, this finding suggests that cortical tissue rated by MRI criteria as being infarcted can still be-at least partially-viable because necrotic tissue would be unable to generate CSD.3 Moreover, it is interesting that the CSD propagated over 3 gyri and in each gyrus, it induced different flow responses: in the most peripheral gyrus, a hyperemic response was followed by lasting oligemia. In the intermediate gyrus, a hyperemic flow response with early return to baseline flow occurred. In the gyrus closest to the infarct core, we detected a lasting hyperemia (table 1, CSD no. 6c). Such hyperemic flow responses to CSD could be protective during this delayed time period because experimental evidence suggests that they alleviate the tissue acidosis.35 But this may have to be weighed against the deleterious effects of the neuronal calcium surge and other direct unfavorable consequences of the CSD process for neurons and astrocytes such as mitochondrial depolarization and release of excitotoxic factors.

In the present human study, we also observed an IOS typical of CSD, preceding the hemodynamic response. This signal was acquired from the unfiltered backscatter photo image. The IOS may represent ionic shifts, changes in blood volume or oxygen delivery, potassium accumulation, or cell swelling.<sup>36</sup> Although the time course of the IOS signal is slower than the changes in membrane potential during CSD,<sup>14,16,18,36</sup> the IOS is assumed to be the best imaging parameter for detecting the front of the CSD. Not every hemodynamic response was, however, preceded by an IOS, which was possibly due to technical reasons in the operating room such as ambient light fluctuations or patient movements.

The baseline cortical CBF is regulated by changes in the tone of cerebral resistance vessels, including the pial arteries. Experimentally, diameter changes of these arteries are easy to assess by imaging methods during CSD.<sup>11</sup> In order to detect them in the human brain, we measured the external diameter of pial vessels close to the area undergoing CSD. However, apart from CSD no. 7 (figure 4), no changes in pial vessel diameter were recorded. This may be explained by the following: 1) only a minority of the resistance vessels is visible at the brain surface, 2) identifying their exact vascular territories is difficult, and 3) vessel diameter changes might occur below image resolution.

LF-VF occur superimposed on the regulation of local tissue perfusion and seem to reflect resting

neural activity.<sup>19</sup> Consistently, CSD not only causes a depolarization block of the resting neuronal activity (spreading depression of spontaneous activity) but also a suppression of LF-VF.<sup>13</sup> Thus, the spreading suppression of LF-VF we observed here further confirmed that CSD was the underlying mechanism of the propagating hemodynamic changes.

Our data describe the spatiotemporal hemodynamic and IOS changes associated with CSD in patients with MHS. In contrast to experimental findings that observed CSDs invading more or less the entire hemisphere, we found multiple CSDs with both hyperemic and hypoemic hemodynamic responses that appeared confined to smaller peri-infarct regions. Whether CSDs are protective or deleterious in the delayed period between 12 and 43 hours after stroke onset remains unclear in the present study. This deserves further investigation with particular focus on the polarity of the hemodynamic responses in relation to infarct progression.

#### AUTHOR CONTRIBUTIONS

J. Woitzik, R. Graf, A.J. Strong, J.P. Dreier, and P. Vajkoczy conceived, designed, and supervised the trial. J. Woitzik, N. Hecht, A. Pinczolits, N. Sandow, S. Major, M.K.L. Winkler, S. Weber-Carstens, C. Dohmen, and J.P. Dreier obtained and analyzed the data. J. Woitzik wrote the first draft of the manuscript. All authors were involved in interpretation of the data and critical revision of the manuscript and approved the final report.

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#### DISCLOSURE

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#### REFERENCES

1. Woitzik J, Back T, Thome C. Flow-dependent versus spreading-like impairment of brain tissue integrity during

focal cerebral ischemia and its consequences for neuroprotective strategies. Front Biosci 2008;13:1500–1506.

- Leão AAP. Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944;7:359–390.
- Dreier JP. The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat Med 2011;17:439–447.
- Mies G, Iijima T, Hossmann KA. Correlation between peri-infarct DC shifts and ischaemic neuronal damage in rat. Neuroreport 1993;4:709–711.
- Dijkhuizen RM, Beekwilder JP, van der Worp HB, Berkelbach van der Sprenkel JW, Tulleken KA, Nicolay K. Correlation between tissue depolarizations and damage in focal ischemic rat brain. Brain Res 1999;840:194–205.
- Takano K, Latour LL, Formato JE, et al. The role of spreading depression in focal ischemia evaluated by diffusion mapping. Ann Neurol 1996;39:308–318.
- Back T, Ginsberg MD, Dietrich WD, Watson BD. Induction of spreading depression in the ischemic hemisphere following experimental middle cerebral artery occlusion: effect on infarct morphology. J Cereb Blood Flow Metab 1996;16:202–213.
- Busch E, Gyngell ML, Eis M, Hoehn-Berlage M, Hossmann KA. Potassium-induced cortical spreading depressions during focal cerebral ischemia in rats: contribution to lesion growth assessed by diffusion-weighted NMR and biochemical imaging. J Cereb Blood Flow Metab 1996;16:1090–1099.
- Dohmen C, Sakowitz OW, Fabricius M, et al. Spreading depolarizations occur in human ischemic stroke with high incidence. Ann Neurol 2008;63:720–728.
- Gloor P. Migraine and regional cerebral blood flow. Trends Neurosci 1986;9:21.
- Shin HK, Dunn AK, Jones PB, Boas DA, Moskowitz MA, Ayata C. Vasoconstrictive neurovascular coupling during focal ischemic depolarizations. J Cereb Blood Flow Metab 2006;26:1018–1030.
- Nakamura H, Strong AJ, Dohmen C, et al. Spreading depolarizations cycle around and enlarge focal ischaemic brain lesions. Brain 2010;133:1994–2006.
- Dreier JP, Major S, Manning A, et al. Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. Brain 2009;132:1866–1881.
- Strong AJ, Anderson PJ, Watts HR, et al. Peri-infarct depolarizations lead to loss of perfusion in ischaemic gyrencephalic cerebral cortex. Brain 2007;130:995–1008.
- Woitzik J, Dreier JP, Hecht N, et al. Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2011;32:203–212.
- Yoon RS, Tsang PW, Lenz FA, Kwan HC. Characterization of cortical spreading depression by imaging of intrinsic optical signals. Neuroreport 1996;7:2671–2674.
- Hecht N, Woitzik J, Dreier JP, Vajkoczy P. Intraoperative monitoring of cerebral blood flow by laser speckle contrast analysis. Neurosurg Focus 2009;27:E11.
- Kumagai T, Walberer M, Nakamura H, et al. Distinct spatiotemporal patterns of spreading depolarizations during early infarct evolution: evidence from real-time imaging. J Cereb Blood Flow Metab 2011;31:580–592.
- Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8:700–711.

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- Lauritzen M. Pathophysiology of the migraine aura: the spreading depression theory. Brain 1994;117:199–210.
- Oliveira-Ferreira AI, Winkler MKL, Reiffurth C, Milakara D, Woitzik J, Dreier JP. Spreading depolarization, a pathophysiological mechanism of stroke and migraine aura. Future Neurol 2012;7:45–64.
- 22. Bosche B, Graf R, Ernestus RI, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol 2010;67:607–617.
- Dunn AK, Bolay H, Moskowitz MA, Boas DA. Dynamic imaging of cerebral blood flow using laser speckle. J Cereb Blood Flow Metab 2001;21:195–201.
- Takeda Y, Zhao L, Jacewicz M, Pulsinelli WA, Nowak TS Jr. Metabolic and perfusion responses to recurrent periinfarct depolarization during focal ischemia in the spontaneously hypertensive rat: dominant contribution of sporadic CBF decrements to infarct expansion. J Cereb Blood Flow Metab 2011;31:1863–1873.
- Leão AAP. Pial circulation and spreading depression of activity in cerebral cortex. J Neurophysiol 1944;7:391–396.
- Sukhotinsky I, Yaseen MA, Sakadzic S, et al. Perfusion pressure-dependent recovery of cortical spreading depression is independent of tissue oxygenation over a wide physiologic range. J Cereb Blood Flow Metab 2010;30: 1168–1177.
- Takano T, Tian GF, Peng W, et al. Cortical spreading depression causes and coincides with tissue hypoxia. Nat Neurosci 2007;10:754–762.
- Lauritzen M, Jorgensen MB, Diemer NH, Gjedde A, Hansen AJ. Persistent oligemia of rat cerebral cortex in the wake of spreading depression. Ann Neurol 1982;12: 469–474.
- 29. Florence G, Dahlem MA, Almeida AC, Bassani JW, Kurths J. The role of extracellular potassium dynamics

in the different stages of ictal bursting and spreading depression: a computational study. J Theor Biol 2009; 258:219–228.

- Nedergaard M, Astrup J. Infarct rim: effect of hyperglycemia on direct current potential and [14C]2-deoxyglucose phosphorylation. J Cereb Blood Flow Metab 1986;6:607–615.
- Vespa PM, McArthur D, O'Phelan K, et al. Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study. J Cereb Blood Flow Metab 2003;23:865–877.
- Hopwood SE, Parkin MC, Bezzina EL, Boutelle MG, Strong AJ. Transient changes in cortical glucose and lactate levels associated with peri-infarct depolarisations, studied with rapid-sampling microdialysis. J Cereb Blood Flow Metab 2005;25:391–401.
- 33. Dreier JP, Ebert N, Priller J, et al. Products of hemolysis in the subarachnoid space inducing spreading ischemia in the cortex and focal necrosis in rats: a model for delayed ischemic neurological deficits after subarachnoid hemorrhage? J Neurosurg 2000;93:658–666.
- 34. Klingebiel R, Friedman A, Shelef I, Dreier JP. Clearance of a status aurae migraenalis in response to thrombendarterectomy in a patient with high grade internal carotid artery stenosis. J Neurol Neurosurg Psychiatry 2008;79:89–90.
- 35. Oliveira-Ferreira AI, Milakara D, Alam M, et al. Experimental and preliminary clinical evidence of an ischemic zone with prolonged negative DC shifts surrounded by a normally perfused tissue belt with persistent electrocorticographic depression. J Cereb Blood Flow Metab 2010;30: 1504–1519.
- Haglund MM, Ojemann GA, Hochman DW. Optical imaging of epileptiform and functional activity in human cerebral cortex. Nature 1992;358:668–671.

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\*CDC. Vital Signs: Overdoses of Prescription Opioid Pain Relievers–United States, 1999–2008. MMWR 2011;60:1–6



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