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PRACTICAL PEARL

The Hemodynamic Response of Spreading Depolarization Observed by Near Infrared Spectroscopy After Aneurysmal Subarachnoid Hemorrhage

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Abstract
Background Electrocorticography (ECoG) in brain-injured patients allows to detect spreading depolarization, a potential mechanism of secondary ischemia. Here, we describe the relationship of spreading depolarization with changes in cerebral hemodynamics using a brain tissue probe applying near infrared spectroscopy (NIRS).
Methods Simultaneous ECoG and NIRS monitoring was performed in a patient with severe aneurysmal subarachnoid hemorrhage. Changes in cerebral blood oxygenation and regional cerebral blood volume were studied before and after the occurrence of spreading depolarization. Cerebral blood flow measurements were performed daily using an indocyanine green dye dilution mode.
Results Single events of spreading depolarizations demonstrated with transient hyperoxic responses and increase in cerebral blood volume. On the other hand, temporal clusters of recurrent spreading depolarizations were associated with prolonged hypoxic responses and decrease in cerebral blood volume. Cerebral blood flow measurements showed higher values before compared to after onset of spreading depolarization (33.7 ± 8.4 vs. 24.2 ± 4.5 ml/100 g/min).
Conclusions The findings suggest that NIRS monitoring in the cerebral white matter might reflect the hemodynamic signature of spreading depolarization detected by ECoG recordings. This is of potential interest for the further development of both neuromonitoring methods.

Keywords Electrocorticography · Spreading depolarization · Near infrared spectroscopy · Indocyanine green dye dilution · Cerebral oxygenation · Cerebral blood flow

Introduction

Spreading depolarization (SD) is a dramatic failure of brain ion homeostasis that propagates across the cerebral gray matter at a characteristic velocity of 2–5 mm/min. A large negative shift of the extracellular direct current potential is the most distinctive characteristic of SD in electrocorticogram (ECoG) [1]. In otherwise healthy brain tissue, SD is associated with an increase in cerebral blood flow (CBF) to facilitate the delivery of energy substrates required for reestablishment of ionic gradients and repolarization [2]. However, under conditions of energy compromise such as ischemia or hypoxia, SD may lead to a reduction in CBF and worsen brain damage [3]. Recently, it was observed that clusters of recurrent SDs are associated with progressive ischemic damage in patients with aneurysmal subarachnoid hemorrhage (aSAH) [4–6]. In a first patient, we show the relationship of SD with changes in cerebral hemodynamics and oxygenation using a brain tissue probe applying near infrared spectroscopy (NIRS) in parallel to ECoG recordings.

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Materials and Methods

The report is part of the project MZmo-218/2012 approved by the ethics committee of the Medical Faculty Heidelberg, Germany. Informed consent was obtained from both the legal representative and patient after regaining consciousness.

Case History

A 53-year-old female presented comatose with aSAH (World Federation of Neurological Surgeons grade 5) caused by a ruptured aneurysm of the left middle cerebral artery bifurcation. Initial computer tomography demonstrated intraparenchymal and intraventricular hemorrhage (Fisher score 4) leading to acute hydrocephalus requiring an external ventricular drainage.

Procedure

The patient underwent emergency craniotomy for aneurysm clipping. In addition to routine monitoring, a subdural 8-contact linear electrode strip (Wyler, 5/10 mm, Ad-Tech Medical, Racine, USA) was placed on the cerebral cortex accessible through craniotomy as previously described (Fig. 1) [7]. Furthermore, a brain tissue probe for combined intracranial pressure (ICP) and NIRS monitoring (NeMo Probe®, NeMoDevices AG, Zurich, Switzerland) was inserted into the ipsilateral frontal white matter via a skull bolt kit (Licox IM2, Integra LifeScience, Ratingen, Germany).

Multimodal Neuromonitoring

ECoG electrodes were connected to an amplifier in a monopolar fashion with 8 active channels (sampling rate: 400 Hz, time constant: 100 ms, upper/lower frequency limits: 0.01/200 Hz; Octal Bioamplifier ML138 and Powerlab 16, ADInstruments Pty Ltd, Castle Hill, Australia) and data were analyzed with the LabChart-7 software (ADInstruments). SDs were defined as a sequential onset of slow potential changes propagating along the ECoG strip [8]. Clustered events were defined as $\geq$2 SDs within 3 h.

The NIRS probe is used for ICP monitoring and for determination of parameters of cerebral hemodynamics and oxygenation [9]. The sending and receiving fiberoptics within the probe were connected to a four-wavelength near infrared spectrometer (NeMo Control Unit®, NeMo Devices AG). The technique of NIRS has previously been described in detail [10, 11]. Relative concentration changes of the chromophores oxyhemoglobin (Hboxy) and deoxyhemoglobin (Hbdeoxy) were measured in arbitrary units (a.u.) as a deflection from the baseline. Data were obtained every 2 s using a bedside computer containing pre-installed software (NeMo Monitor®, NeMo Devices AG). The hemoglobin difference (Hbdiff = Hboxy - Hbdeoxy) and the total hemoglobin concentration (Hbtotal = Hboxy + Hbdeoxy) were considered surrogate parameters of cerebral blood oxygenation and regional cerebral blood volume, respectively. CBF measurements were performed daily using a combined NIRS and indocyanine green (ICG) dye dilution mode as described in detail elsewhere [12].

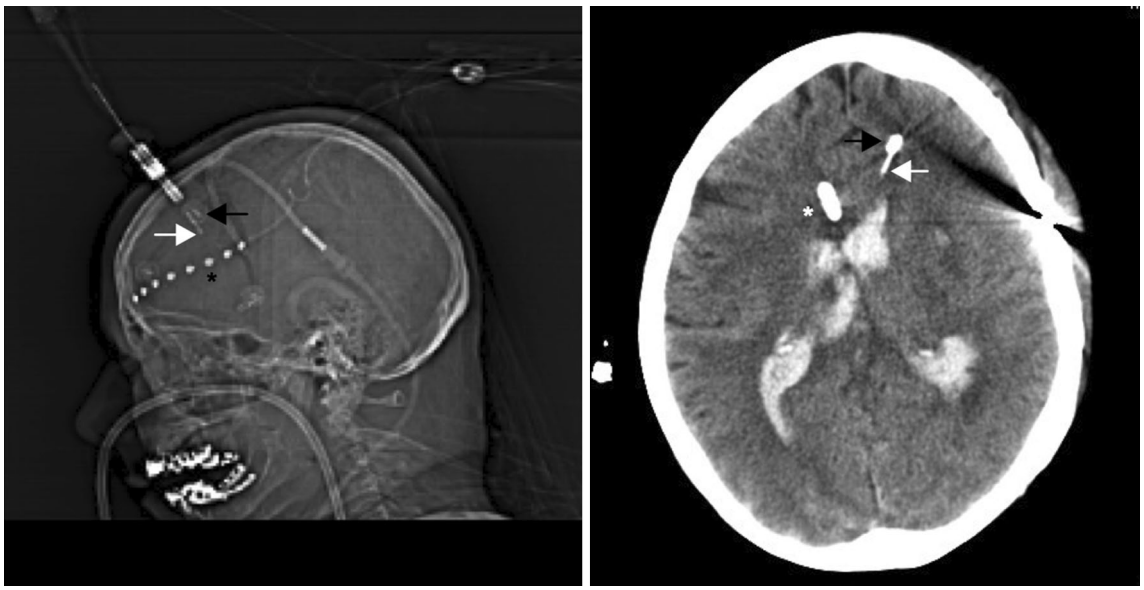

Fig. 1 Computer tomography scan (sagittal bone and axial soft tissue window) showing the NIRS probe (*black arrow*), brain tissue oxygen probe (*white arrow*), and ECoG strip (*black asterisk*). An external ventricular drainage (*white asterisk*) was inserted due to occlusive hydrocephalus

Continuous NIRS data (Hboxy, Hbdeoxy, Hbdiff, and Hbtotal) were averaged every 60 s to explore the response to SD. All quantitative data are expressed as mean ± standard error of the mean (SEM).

Hospital Course

Postoperatively, the patient remained sedated (propofol, midazolam, fentanyl) and on ventilator support in the neurointensive care unit. Intermittent osmotic therapy (mannitol and hypertonic NaCl-hydroxyethyl-starch solution) was added on day 3 after aSAH due to several episodes of intracranial hypertension (ICP > 20 mmHg). From day 5 after aSAH, SD events were observed spreading spatially along the electrodes at a characteristic speed of 2.8 ± 0.9 mm/min. The patient was otherwise stable. Cerebral angiography on day 8 revealed mild-to-moderate vasospasm of the left middle cerebral artery (M2 segment), which was treated periprocedurally with intra-arterial nimodipine and hemodynamic augmentation.

Outcome

There was no evidence of cerebral infarction on computer tomography at hospital discharge (28 days after aSAH). At this time, the patient was awake and following commands, but with an accentuated frontal lobe syndrome (therefore modified Rankin Score 4). At 3 months after aSAH the modified Rankin score was 2, and the patient was able to look after own affairs without assistance.

Results

In total, 12 SDs were identified during 103 h of simultaneous ECoG and NIRS monitoring (Fig. 2). Single and clustered SDs were recorded in 6 events each. 7 of 12 SDs were associated with a transient hyperoxic response (SD No. 1, 2, 3, 6, 8, 11, 12) and 3 with a prolonged hypoxic response (SD No. 4, 5, 7). In 2 SDs no specific change in NIRS oximetry was observed. The hyperoxic response demonstrated an increase in Hboxy and decrease in Hbdeoxy lasting up to 40 min after SD. Cerebral blood oxygenation, reflected by the Hbdiff, increased transiently during the monitoring period without changes in cerebral perfusion pressure. Regional cerebral blood volume, reflected by the total hemoglobin concentration (Hbtotal), increased in parallel to the observed increase in ICP. The hypoxic response showed an increase in Hbdeoxy and decrease in Hboxy within 30 min after SD without recovery of Hboxy to baseline values at 90 min after SD. A long-lasting decrease in cerebral blood oxygenation (Hbdiff) was observed although cerebral perfusion pressure slightly increased during the monitoring period. Regional cerebral blood volume (Hbtotal) decreased after SD and was accompanied by a decrease in ICP. It has to be noted, that 3 out of 6 clustered SDs were associated with the hypoxic response, whereas all single SDs were associated with the hyperoxic response.

A total of 15 CBF measurements demonstrated on average higher values on days before ($n = 10$) compared to after ($n = 5$) the onset of SD (33.7 ± 8.4 and 24.2 ± 4.5 ml/100 g/min, respectively).

Discussion

NIRS measurements are based upon the finding that light in the near infrared region penetrates biological tissue and is absorbed differently by the chromophores Hboxy and Hbdeoxy [11]. Recently, NIRS has been shown instrumental in detection and treatment of secondary ischemia after aSAH [13]. Moreover, the utility of NIRS has been extended with a light absorbing dye dilution mode applying ICG for determination of cerebral hemodynamics [12]. After central venous injection of ICG, the intravascular passage and distribution of the tracer can be quantified for calculation of CBF. However, the clinical application of conventional NIRS with optodes applied over the skin is controversially discussed, because extracerebral tissues (skin, skull, and cerebrospinal fluid) contaminate the light signal. Therefore, a brain tissue probe for ICP monitoring has been supplied with optical fibers for NIRS [9]. The NIRS probe brings the light directly into the region of interest and carries the reflected light back to the sensor, so that "extracerebral contamination" can be ruled out completely. The NIRS probe has the same dimensions and stiffness as ordinary ICP probes. Thus, for patients with severe brain injury where ICP monitoring is indicated, the NIRS probe offers the benefit of enhanced cerebrovascular hemodynamic monitoring without an additional risk.

We demonstrate for the first time NIRS monitoring during the occurrence of SD in a patient with aSAH. SD likely induced the observed changes cerebral blood oxygenation, because cerebral perfusion pressure remained stable during the monitoring period. However, the time evolution for oxygen changes during SD remains elusive based on the spatial distance between the NIRS probe and ECoG strip. Experimental evidence suggests four different types of CBF responses to SD including (1) transient monophasic increases, (2) biphasic changes with an initial decrease followed by an increase, (3) monophasic transient decreases, and (4) permanent reduction in perfusion below the ischemic threshold [3]. It has been shown that SD induces vasodilation as a physiological hemodynamic response, whereas severe vasoconstriction is coupled to SD when there is local

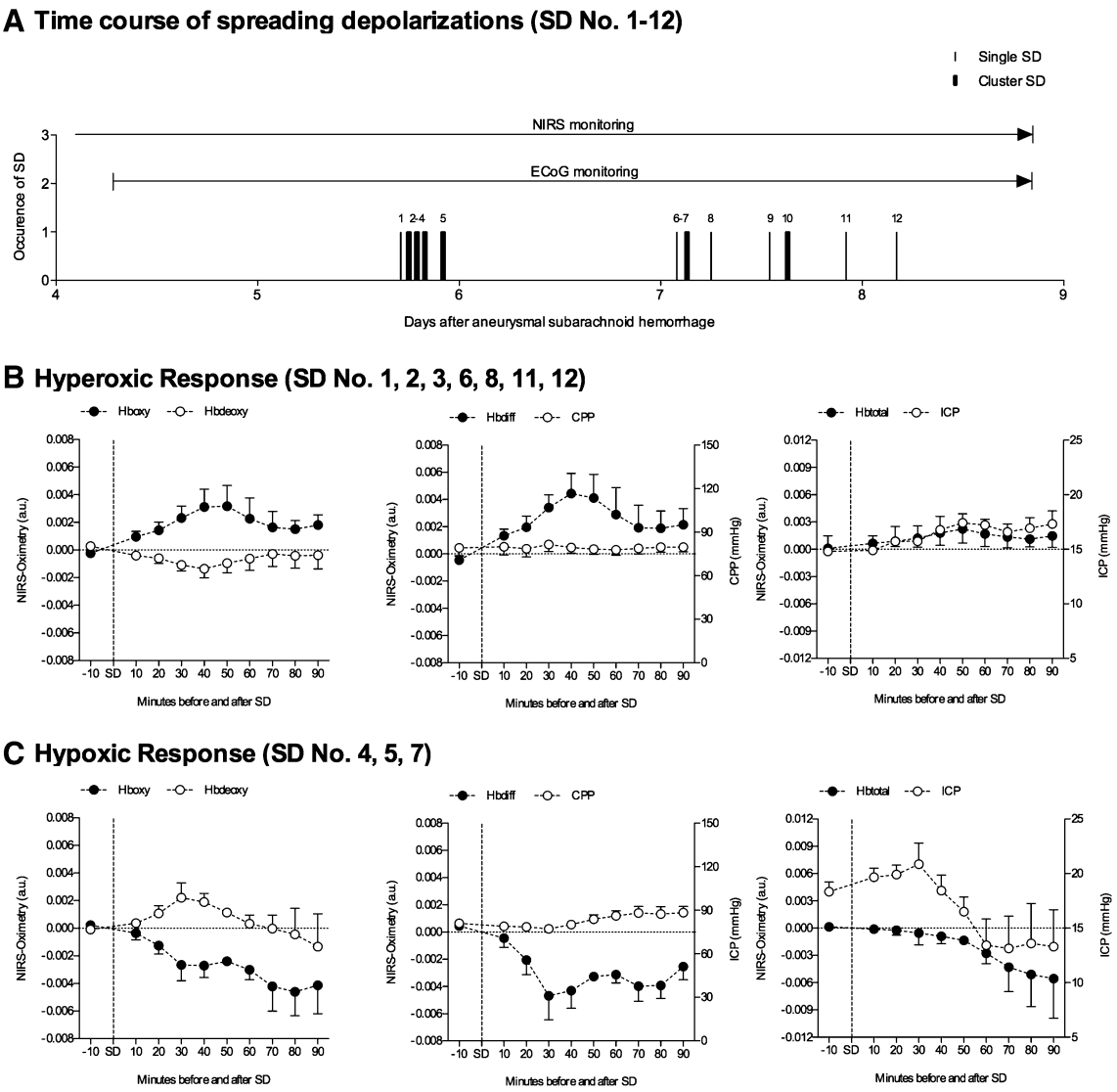

Fig. 2 **a** Time course of single and clustered spreading depolarizations. **b** Hyperoxic response during spreading depolarization. **c** Hypoxic response during spreading depolarization. *NIRS* near infrared spectroscopy, *ECoG* electrocorticogram, *SD* spreading depolarization, *Hboxy* oxyhemoglobin, *Hbdeoxy* deoxyhemoglobin, *Hbdiff* hemoglobin difference, *Hbtotal* total hemoglobin concentration, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure

dysfunction of the microvasculature [14–16]. These findings closely correlate with SD-induced changes in cerebral oxygenation in patients with aSAH [4]. In particular, clustered events of SD have been associated with a decrease in perfusion and increased risk of neurological worsening [5]. In this particular study a customized combination of laser-doppler flow probes connected to ECoG strip electrodes was used. This was further corroborated by the findings in our case. To further elucidate the hemodynamic signature of SD, the NIRS probe can be considered in selected patients with brain injury in whom SDs are detected using ECoG. The integration of optical fibers for NIRS into the ECoG strip might prove helpful in the future to study the exact temporal pattern of hemodynamic changes during events of SD in the human brain.

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References

1. Hartings JA, Watanabe T, Dreier JP, Major S, Vendelbo L, Fabricius M. Recovery of slow potentials in AC-coupled electrocorticography: application to spreading depolarizations in rat and human cerebral cortex. J Neurophysiol. 2009;102:2563–75.
2. Somjen GG. Mechanisms of spreading depression and hypoxic spreading depression-like depolarization. Physiol Rev. 2001;81:1065–96.
3. 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.

4. Bosche B, Graf R, Ernestus RI, et al. Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol. 2010;67:607–17.
5. 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;132:1866–81.
6. Sakowitz OW, Santos E, Nagel A, et al. Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. Stroke. 2013;44:220–3.
7. Strong AJ, Fabricius M, Boutelle MG, et al. Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke. 2002;33:2738–43.
8. Fabricius M, Fuhr S, Bhatia R, et al. Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. Brain. 2006;129:778–90.
9. Keller E, Froehlich J, Muroi C, Sikorski C, Muser M. Neuromonitoring in intensive care: a new brain tissue probe for combined monitoring of intracranial pressure (ICP) cerebral blood flow (CBF) and oxygenation. Acta Neurochir Suppl. 2011;110:217–20.
10. McCormick PW, Stewart M, Goetting MG, Dujovny M, Lewis G, Ausman JI. Noninvasive cerebral optical spectroscopy for monitoring cerebral oxygen delivery and hemodynamics. Crit Care Med. 1991;19:89–97.
11. Jobsis FF. Non-invasive, infra-red monitoring of cerebral O_2 sufficiency, bloodvolume, HbO_2-Hb shifts and bloodflow. Acta Neurol Scand Suppl. 1977;64:452–3.
12. Keller E, Nadler A, Alkadhi H, Kollias SS, Yonekawa Y, Niederer P. Noninvasive measurement of regional cerebral blood flow and regional cerebral blood volume by near-infrared spectroscopy and indocyanine green dye dilution. Neuroimage. 2003;20:828–39.
13. Mutoh T, Ishikawa T, Suzuki A, Yasui N. Continuous cardiac output and near-infrared spectroscopy monitoring to assist in management of symptomatic cerebral vasospasm after subarachnoid hemorrhage. Neurocrit Care. 2010;13:331–8.
14. Lauritzen M. Pathophysiology of the migraine aura. The spreading depression theory. Brain. 1994;117(Pt 1):199–210.
15. Dreier JP, Korner K, Ebert N, et al. Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space. J Cereb Blood Flow Metab. 1998;18:978–90.
16. 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;26:1018–30.