Case Studies

Continuous Monitoring of Spreading Depolarization and Cerebrovascular Autoregulation after Aneurysmal Subarachnoid Hemorrhage

Kazutaka Sugimoto, MD, Satoshi Shirao, MD, Hiroyasu Koizumi, MD, Takao Inoue, PhD, Fumiaki Oka, MD, Yuichi Maruta, PhD, Eiichi Suehiro, MD, Hirokazu Sadahiro, MD, Takayuki Oku, MD, Hiroshi Yoneda, MD, Hideyuki Ishihara, MD, Sadahiro Nomura, MD, and Michiyasu Suzuki, MD

> Delayed cerebral ischemia (DCI) is a prominent complication after aneurysmal subarachnoid hemorrhage (aSAH). Although vasospasm of proximal cerebral arteries has been regarded as the main cause of DCI, vasospasm of distal arteries, microthrombosis, impaired autoregulation, cortical spreading depolarization (CSD), and spreading ischemia are thought to be involved in DCI after aSAH. Here, we describe a patient with aSAH in whom CSD and cerebrovascular autoregulation were evaluated using simultaneous electrocorticography and monitoring of the pressure reactivity index (PRx) after surgical clipping of a ruptured posterior communicating artery aneurysm. In this patient, a prolonged duration of CSD and elevation of PRx preceded delayed neurological deficit. Based on this observation, we propose a relationship between these factors and DCI. Assessment of cerebrovascular autoregulation may permit detection of the inverse hemodynamic response to cortical depolarization. Detection of DCI may be achieved through simultaneous monitoring of CSD and PRx in patients with aSAH. Key Words: Subarachnoid hemorrhage-cortical spreading depolarization-delayed cerebral ischemia—spreading ischemia—vasospasm—cerebrovascular autoregulation.

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Introduction

Delayed cerebral ischemia (DCI) and early brain injury induced by initial hemorrhage are major lethal complications in patients with subarachnoid hemorrhage (SAH).¹² The risk for DCI correlates with the amount of blood in the subarachnoid space and DCI is presumably caused by erythrocyte products in the subarachnoid space, but the pathophysiology is complex.³ Delayed vasospasm of major cerebral arteries has been regarded as the main cause of DCI, but chronic vasospasm of distal arteries, microthrombosis, impaired autoregulation, spreading

From the Department of Neurosurgery, Yamaguchi University School of Medicine, Ube, Yamaguchi, Japan.

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Address correspondence to Satoshi Shirao, MD, Department of Neurosurgery, Yamaguchi University School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi, 755-8505, Japan. E-mail: shirao@ yamaguchi-u.ac.jp.

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depolarization, and spreading ischemia are possible complementary factors in the pathogenesis of DCL^{2,4-9}

Cortical spreading depolarization (CSD) is characterized by near-complete breakdown of ion gradients, near-complete sustained depolarization in individual recordings of neurons, extreme shunt of neuronal membrane resistance, loss of electrical activity, and neuron swelling and distortion of dendritic spines.5 CSD is observed as a prominent negative slow potential change (SPC) measured in the low-frequency or direct current (DC) range in electrocorticography (ECoG).¹⁰ CSD causes brain electrical silence, which is referred to as spreading depression of brain electrical activity¹¹ and is observed as a silencing of spontaneous activity measured in the high frequency or alternating current (AC) range in ECoG. CSD is induced by various noxious conditions but can also occur in healthy naive tissue.⁵ Resistance vessels respond to CSD by transient hyperperfusion, which is a physiological hemodynamic response (spreading hyperemia) in healthy tissue, but severe hypoperfusion (spreading ischemia, inverse response) due to changes in vascular reactivity in tissue at the risk of cell death from various noxious conditions leads to DCI in patients with SAH.^{5,12-14}

The pressure reactivity index (PRx) is a moving correlation coefficient between the mean arterial blood pressure (ABP) and intracranial pressure (ICP) that reflects cerebrovascular autoregulation.^{15,16} PRx has recently been reported to be useful for clinical monitoring of patients with severe SAH and traumatic brain injury.^{17,18}

We describe a patient with aneurysmal subarachnoid hemorrhage (aSAH) in whom CSD and cerebrovascular autoregulation were evaluated using simultaneous ECoG and PRx monitoring after surgical clipping of a ruptured posterior communicating artery aneurysm.

Protocol of CSD and PRx Monitoring

The present study was approved by Yamaguchi University Hospital, Ube, Yamaguchi, Japan. The research protocol was approved by the Center for Clinical Research, Yamaguchi University Hospital. Informed consent for the study was obtained after a clinical decision had been made to perform clipping surgery.

Placement of Electrode and Microsensor

Clipping surgery allowed placement of a single, linear, 6-pole (platinum) subdural electrode (SD-6P; Ad-Tech Medical Instrument Corp., Racine, WI) on the ipsilateral frontal lobe through craniotomy or via a burr-hole.¹³ An intraparenchymal ICP sensor (Codman MicroSensor Basic Kit; Codmann & Shurtleff, Raynham, MA) was placed in the same manner.¹⁹

ECoG

ECoG was performed continuously in 5 active channels from the 6-pole (linear array) subdural electrode. Electrode 6 served as ground, whereas electrodes 1-5 (sealed brain contacts, 1.0-cm spacing) were connected in a sequential unipolar fashion to a NicoletOne (.016-45.0 Hz) system (CareFusion, Yorba Linda, CA), each referenced to an ipsilateral subgaleal electrode (Disposable Subdermal Needle Electrode; Nihon Koden, Tokyo, Japan). The DC-ECoG of electrodes 1 and 3 was also recorded using a MT-BA-B3S-R2 (0-45 Hz) system (Melon Technos, Kanagawa, Japan). DC-ECoG was sampled at 200 Hz and recorded and reviewed using a PowerLab 16/SP analog/ digital converter, Chart-7 software (ADInstruments, Bella Vista, New South Wales, Australia). ECoG (.016-45.0 Hz) was also reviewed using Chart-7 software (ADInstruments).

PRx Monitoring

Continuous ICP monitoring was achieved using an intraparenchymal ICP sensor connected to an ICP transducer (Codman ICP Express, Codmann & Shurtleff).¹⁹ ABP was continuously monitored from the radial artery using a standard monitoring kit (TruWave; Edwards Lifesciences, Irvine, CA). The ABP sensor was placed at the cardiac level and signals were viewed on a bedside monitor (Life Scope, Nihon Koden). The continuous ICP and ABP signals were sampled at 200 Hz and recorded and reviewed using a PowerLab 16/SP analog/digital converter and Chart-7 software (ADInstruments).

Data Analysis

CSD was defined by sequential onset in adjacent channels of a propagating SPC. SPC is expressed as a negative DC potential change (TrueDC) and can be detected using AC amplifiers (higher frequency limit: .05 Hz, near DC).^{20,21} Criteria for SPC detected using AC amplifiers are a bior triphasic change in potential with a duration of 2-5 minutes and an amplitude of .06-3.0 mV.12 CSDs were classified as single or clusters (CSDs with an interval <2 hours).^{13,22,23} Simultaneous high-frequency ECoG depression was a priori defined by a rapidly developing reduction of the power of the ECoG amplitude by at least 50%.²¹ The duration of the depression period of the highfrequency ECoG activity was measured as the interval between onset of depression and restoration of activity using the integral of the power of the bandpass-filtered activity (bandpass: .5-45 Hz; time constant decay, 60 seconds).^{13,20}

PRx was calculated every 5 minutes using a 5-second moving window as a Pearson correlation coefficient between the mean ABP and mean ICP averaged over 5-second periods.¹⁸ The mean PRx for 24 hours was calculated. ECoG and PRx monitoring were started as soon as possible after surgery. We show the association between

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Figure 1. CT and MRI showing infarctions associated with delayed cerebral ischemia. (A and B) Initial CT for Fisher group 3 aneurysmal subarachnoid hemorrhage. (C) CT scout view showing the electrode strip placed on the cortex of the right frontal lobe (arrow). (D) Diffusion-weighted MRI on day 1 showed infarction in the right PCom and PCA territories associated with surgery. (E and F) FLAIR MRI on day 1 showed infarction in the right PCom and PCA territories associated with surgery, but no infarction in the right MCA area. (G) CT on day 4 showed hemorrhagic infarction with ventricular hemorrhage in the right PCA territory. (H and I) CT on day 7 showed no new lesion. (J) CT on day 10 showed a new low-density area in the right MCA territory (arrow). (K and L) FLAIR image on day 20 showed a new scattering abnormal signal in the right MCA area (arrow). Abbreviations: CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; PCom, posterior communicating artery.



the average duration of the ECoG depression period per CSD on each day (duration of spreading depression) and PRx.

Case Report

A 64-year-old female had World Federation of Neurosurgical Societies Grade 1 and Fisher group 3 SAH based on a computed tomography (CT) scan at admission (Fig 1, A,B). On day 0 (onset of SAH), CT angiography (Fig 2, left) revealed a ruptured right posterior communicating artery aneurysm, and surgical clipping was performed on the same day. After clipping, external ventricular and cisternal drains were placed, and an electrode strip and ICP sensor were also placed on the cortex of the right frontal lobe (Fig 1, C). After surgery, the patient had left-sided hemiparesis (manual muscle testing [MMT] score 0). Diffusion-weighted and fluid-attenuated inversion recovery magnetic resonance imaging (MRI) on day 1 showed infarction in the right posterior communicating artery and posterior cerebral artery territories (Fig 1, D-F), indicating an ischemic complication of surgery. ECoG and PRx monitoring over the right middle frontal gyrus were started on day 1.

Follow-up CT on day 4 showed hemorrhagic infarction with ventricular hemorrhage in the right posterior



Figure 2. CT angiography and DSA showing vasospasm associated with delayed cerebral ischemia. Left: CT angiography on day 0 revealed a ruptured right posterior communicating artery aneurysm. Right: DSA on day 9 showed severe vasospasm of the right parietal branch from the middle cerebral artery (M2) inferior trunk. The arrow points to a vasospasm of the right parietal branch (M2) inferior trunk. Abbreviations: CT, computed tomography; DSA, digital subtraction angiography; H, cranial view.

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Figure 3. ECoG recording (full scale: 400 μ V) in a monopolar fashion. Cortical spreading depolarization started to occur on day 2. The upper 5 traces show propagation of slow potential change (near direct current, low-pass filtered ECoG activity, higher frequency limit: .05 Hz) in each electrode. The lower 5 traces show simultaneous high-frequency ECoG depression (cortical spreading depression, bandpass: .5-45.0 Hz). Abbreviation: ECoG, electrocorticography.

cerebral artery territory (Fig 1, G). Left-sided hemiparesis ameliorated (change in MMT score from 0 to 2) until day 4 and there were no apparent episodes indicating new neurological deficits. ECoG on day 2 displayed SPC that indicated spreading depolarization. Depression periods accompanied by the SPC were short (2.5 minutes on day 2 and 3.0 minutes on day 3) (Fig 3). PRx values were .29 on day 1 and .36 on day 2, but then declined gradually from days 2 to 4 (Fig 4).

On day 5, 3 SPCs occurred in DC/AC-ECoG trace 1 and near-DC/AC-ECoG traces 2-6 (subdural electrodes 1-5) in an episode lasting 90 minutes, indicating clusters of CSDs (Fig 5). Traces 7-11 depicted spreading depression of spontaneous activity accompanied by clusters of CSDs in the power of the AC-ECoG at subdural electrodes 1-5. The PRx rose from days 4 to 7 and was .3 or higher on days 6 and 7 (Fig 4). On day 7, some episodes of declining consciousness occurred (Glasgow Coma Scale [GCS] score decreased from 14 to 12) and ICP increased to 20 mmHg. CT did not show a new lesion (Fig 1, H,I); however, the duration of spreading depression on day 7 was 16.9 minutes and the PRx rose to .34 (Fig 4).

On day 9, the level of consciousness declined even further (GCS score decreased from 12 to 7) and digital subtraction angiography showed severe vasospasm of the right parietal branch from the middle cerebral artery (MCA) (M2) inferior trunk (Fig 2, right). The proximal MCA (M1) showed no apparent vasospasm. Superselective intraarterial infusion of fasudil hydrochloride, a Rhoassociated protein kinase inhibitor,²⁴ resulted in little recovery of consciousness after intervention (GCS score





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Figure 5. Clusters of CSD started to appear on day 5. ECoG recording in a monopolar manner. The upper trace is full-band ECoG (bandpass: 0-45 Hz, full scale: 7 mV) of electrode 1, showing a DC potential change 3 times in the 90 minutes shown. The middle 5 traces show the propagation of a slow potential change (near DC, low-pass filtered ECoG activity, higher-frequency limit: .05 Hz, full scale: 400μ V) in each electrode. The lower 5 traces show simultaneous high-frequency ECoG depression (cortical spreading depression, bandpass: .5-45.0 Hz, full scale: 400μ V). CSDs occurred 3 times in this period, reflecting so-called clusters of CSDs. Abbreviations: CSP, cortical spreading depolarization; DC, direct current; ECoG, electrocorticography; PRx, pressure reactivity index; SAH, subarachnoid hemorrhage.

increased from 7 to 8). The duration of spreading depression was shortened on day 10, but was still more than 10 minutes and the PRx was still higher than .2 (Fig 4). These trends continued until day 15 (Fig 4). The CT result on day 10 showed a new low-density area in the right MCA territory (Fig 1, J).

On day 16, the duration of spreading depression was less than 10 minutes and the PRx was lower than .2. On day 20, fluid-attenuated inversion recovery MRI showed a new delayed ischemic infarction in the right MCA territory, including the recording area (Fig 1, K,L). The patient had left-sided hemiparesis (MMT score = 1) and disturbance of consciousness (GCS score = 13). The patient was transferred to another hospital for rehabilitation on day 60.

Discussion

The present study is the first report of simultaneous CSD and PRx monitoring. Prolonged ECoG depression and elevation of PRx preceded vasospasm and DCI in our patient.

The phenomenon of spreading ischemia was discovered in a rat model replicating the delayed condition following subarachnoid hemolysis after SAH.⁴ Decrease of nitric oxide availability combined with CSD causes a change of vascular reactivity and a shift from spreading hyperemia to spreading ischemia.^{4,5} Blood–brain barrier disruption, inflammatory response, oxidative stress, and apoptosis are also common in early brain injury after SAH, and are known to cause endothelial dysfunction and autoregulatory failure.²⁵ Furthermore, experimental evidence suggests that physiological hemodynamic responses occur only when cerebrovascular autoregulation is intact and that pathological inverse responses are associated with progressive autoregulatory impairments.²⁶

Spreading ischemia delays cortical repolarization. Thus, a prolonged negative cortical DC shift and a prolonged ECoG depression are the defining electrophysiological features of spreading ischemia.¹² Severe spreading ischemia is sufficient to induce widespread cortical necrosis in rats.²⁷ In a prospective multicenter study, CSD occurred in 72% of patients with aSAH,¹³ and in a similar study in 13 patients with aSAH, clusters of CSDs with prolonged depression and prolonged CSD were associated with CSD-induced spreading hypoperfusion.¹² In addition, depression periods lasting more than 10 minutes have been associated with a worse outcome, and those lasting more than 60 minutes caused delayed infarctions on CT or MRI.¹³

PRx is useful for clinical monitoring of patients with severe SAH and traumatic brain injury.¹⁷⁻¹⁹ PRx reflects cerebrovascular autoregulation,^{15,16} in which elevation of systemic blood pressure evokes a vasomotor reaction in the cerebrovascular beds to maintain a consistent level of cerebral blood flow.²⁸ This active vasomotor reaction allows ICP to be reduced. Based on this mechanism, ICP is thought to be negatively correlated with systemic blood pressure.²⁸ In cases of severe brain damage with im-

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paired cerebrovascular autoregulation, a passive vasomotor reaction reflects elevated ICP along with increased blood pressure, which gives a positive correlation between these parameters.^{15,19} Rasulo et al¹⁷ found that a PRx above the .2 threshold was useful for the diagnosis of impairment of autoregulation.

In our patient, the PRx was .29 on day 1 and gradually declined from days 2 to 4. This early high index may indicate impairment of autoregulation by initial damage. Subsequent elevation of PRx on days 4-15 coincided with prolonged depression and a new infarction in the right MCA territory. Because CSD may stop at the central sulcus,²² CSDs and prolonged depression detected from day 4 might have been derived from frontal–parietal SAH rather than the occipital hemorrhagic infarction. Thus, we speculate that impairment of autoregulation caused an inverse hemodynamic response to cortical depolarization resulting in DCI.

Experimental evidence suggests that spreading ischemia is augmented and prolonged by a decline in cerebral perfusion pressure, while an artificial cerebral perfusion pressure increase can convert spreading ischemia to an almost normal spreading hyperemic response to CSD.^{27,29} Thus, selective intra-arterial infusion of fasudil might ameliorate spreading ischemia. In our case, superselective intraarterial infusion of fasudil did not decrease PRx but shortened the duration of spreading depression. In addition, the PRx and duration of spreading depression elevated again on day 11. The discrepancy would be caused by the fact that fasudil is cleared quickly from the blood, with a half-life of less than 15 minutes.^{24,30} Further work is needed to assess the relationship between CSD and PRx with DCI after SAH.

In conclusion, assessment of cerebrovascular autoregulation may permit detection of the inverse hemodynamic response to cortical depolarization. Detection of DCI may be achieved through simultaneous CSD and PRx monitoring in patients with aSAH.

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