NEUROVASCULAR COUPLING AND EPILEPSY: HEMODYNAMIC MARKERS FOR LOCALIZING AND PREDICTING SEIZURE ONSET

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Hemodynamic surrogates of epileptic activity are being used to map epileptic foci with PET, SPECT, and fMRI. However, there are few studies of neurovascular coupling in epilepsy. Recent data indicate that cerebral blood flow, although focally increased at the onset of a seizure, may be temporarily inadequate to meet the metabolic demands of both interictal and ictal epileptic events. Transient focal tissue hypoxia and hyperperfusion may be excellent markers for the epileptic focus and may even precede the onset of the ictal event.

In recent years, the field of brain mapping has witnessed the growth of a variety of techniques that use measurements of hemodynamic changes as surrogates for neuronal activity. This development particularly has occurred in the treatment of epilepsy, for which therapeutic decisions are often made based on the results of PET, SPECT, and *f* MRI scans. Hemodynamic signals, generally derived from perfusion and/or oximetry, are attractive since they often can be measured noninvasively. However, accurate interpretation of these data depends on a firm understanding of neurovascular coupling mechanisms in the brain, especially as they pertain to abnormal events such as epilepsy.

Neurovascular Coupling in the Brain during Normal Cortical Processing

The study of neurovascular coupling examines the relationships among neuronal activity, metabolism, tissue and blood oxygenation, and blood flow. It is generally accepted that during normal cortical processing, increases in neuronal activity simultaneously increase the cerebral metabolic rate of oxygen and glucose, leading to an increase in cerebral blood flow (CBF) and cerebral blood volume (CBV), as the brain attempts to perfuse active neurons with oxygenated hemoglobin (1). PET studies of oxygen metabolism and blood flow, a technique with a slow temporal resolution, have demonstrated that increases in CBF occurring 1–2 s after the onset of neuronal activity provide an oversupply of oxygenated hemoglobin (2). Hence, the cerebral metabolic rate of oxygen and CBF are "uncoupled," causing an increase in oxygenated hemoglobin that forms the basis of the blood oxygenation level-dependent (BOLD) signal imaged with *f* MRI (3). More recently, using techniques with higher spatial and temporal resolution—such as optical recording of intrinsic signals (ORIS) (4), imaging spectroscopy (5,6), oxygen-dependent phosphorescence quenching (7), oxygen-sensitive electrodes (8,9), and *f* MRI at 1.5 and 4 Tesla (10,11)—investigators have examined changes in tissue and blood oxygenation that occur within the first few hundred milliseconds after neurons become active. These studies demonstrated a rapid decrease in tissue oxygenation and an increase in deoxygenated hemoglobin that precedes the increase in CBF. This "initial dip," although questioned by some studies (12,13), implies that for a brief period of time after neurons discharge, the brain is mildly ischemic until cerebrovascular autoregulation dilates arterioles to increase CBF.

Neurovascular Coupling in Epilepsy

Epilepsy is an abnormal physiologic state which, unlike normal somatosensory processing, places supra-normal demands on the brain's autoregulatory mechanisms as a result of an enormous increase in the metabolic rate of oxygen following both interictal and ictal events (14). Hence, neurovascular-coupling mechanisms that apply in the normal situation may not be relevant to the epileptic brain. Whether or not CBF is adequate to meet the increased metabolic demands of epilepsy has been a long-standing debate. The initial hypoxia–hypoperfusion hypothesis, derived from histologic similarities between ischemic and epileptic brain damage, proposed that the cell damage following status epilepticus was caused by cerebral anoxia (15–17). Later studies refuted this theory based on findings that the relative increase in CBF was greater than the relative increase in cerebral metabolism (18–20); the cellular damage associated with status epilepticus was not identical to hypoxic injury (21); seizures induced increases, rather than decreases, in venous oxygenation (17,22); the presence of oxidation in the mitochondrial transport chain, NADH, and cytochrome oxidase (23,24); increases

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in tissue pO_2 (25,26); and tissue injury that occurred even in the absence of cerebral anoxia (16,22).

PET and *f*MRI

More recent studies in animals using autoradiography, PET, and *f*MRI, which have limited temporal and spatial resolution, have been contradictory (18,20,27–30). While an increase in perfusion is universally demonstrated, some studies find that perfusion oversupplies metabolism (29,30) while others demonstrate that there is inadequate perfusion to meet metabolic demand (18,20,27,28). Investigators using interictal and ictal spike-triggered *f*MRI on humans, generally report an increase in the BOLD signal consistent with a decrease in deoxygenated hemoglobin and adequate CBF (31–36). However, most *f*MRI studies have been performed on interictal rather than ictal events, which may elicit such a brief focal increase in deoxygenated hemoglobin as to be undetectable without higher strength magnets (31–33,35). Likewise, ictal *f*MRI studies have been done either on generalized spike-and-wave events, which may not elicit an increase in deoxygenated hemoglobin in the cortex (34,36), or without concurrent electrical recordings, rendering the timing of the imaging unclear with respect to the seizure onset (37,38).

Optical Spectroscopy and Oxygen-Sensitive Electrodes

More recently, studies in animals using techniques, such as ORIS and oxygen-sensitive electrodes that have even higher spatial and/or temporal resolution than PET or *f*MRI, have been performed to resolve these persistent questions. Optical spectroscopy uses ORIS at multiple wavelengths to measure blood oxygenation and CBV from large areas of cortex simultaneously with a spatial and temporal resolution that is limited by the specifications of the camera acquiring the data and by the evolution of the signal ($\sim$33 milliseconds and $<$200 μm). This technique is based on variations in the light absorption spectrum of hemoglobin in the oxygenated and deoxygenated state (4). Measurements of deoxygenated hemoglobin and CBV with ORIS have demonstrated a clear increase in deoxygenated hemoglobin, in spite of an increase in CBV, during both interictal and ictal events in animal models of focal epilepsy, indicating that for a variable period of time at the onset of a epileptic event CBF is not adequate to meet metabolic demand (39–42). For interictal events, hemoglobin oxygenation drops for $\sim$3 s, whereas at the beginning of a seizure, the drop in oxygenation can last for tens of seconds. Once the dip ends, there is a dramatic increase in oxygenated hemoglobin, which explains the increase in BOLD signal found with *f*MRI. Confirmation of this finding was achieved by directly measuring tissue pO_2 using oxygen-sensitive electrodes, which demonstrated a decrease in tissue pO_2 at the onset and throughout most of the duration of focal seizures followed by an increase in pO_2 (39).

Whether animal data are relevant to human epilepsy is unclear. However, taking a look back in order to look forward, one can find studies performed as long as 40 years ago in which oxygen-sensitive electrodes were placed within the epileptic focus of human cortex during chronic electrocorticographic monitoring. These studies also showed a decrease in tissue pO_2 during focal human epilepsy (43,44). More recently, similar results were shown with near infrared spectroscopic (NIRS) data measured through the scalp during pediatric epileptic events (45) and using multiwavelength ORIS in human epileptic cortex in the operating room (46,47,55).

Significance

What is the significance of these findings? First, if the transient decrease in hemoglobin oxygenation associated with interictal and ictal events is more focal than the subsequent increase, then imaging techniques that measure the later increase, such as BOLD *f*MRI, may mistakenly localize the epileptic focus or demonstrate a larger area than the onset zone. Higher resolution magnets that concentrate on the earlier decrease in hemoglobin oxygenation may have better localizing value. Second, a decrease in tissue oxygen during epileptic events again raises the possibility of hypoxia-induced tissue damage during prolonged ictal or high-frequency interictal events. Therapeutic intervention to restore cortical oxygenation may prove efficacious. Finally, there is increasing evidence that hemodynamic events may be useful not only for localizing but also for predicting the onset of seizures. This concept was proposed as early as 1933 (48). More recent studies using transcranial Doppler have demonstrated increases in lobar perfusion 20 min before focal as well as generalized spike-and-wave events (49–51). Likewise, both increases (36,45,52) and decreases (53) in tissue oxygenation have been found tens of seconds before seizure onset using *f*MRI and NIRS. ORIS data also have shown focal preictal changes in light reflection in both animal and human models (46,55). These findings raise the intriguing possibility that hemodynamic changes may be useful in predicting seizure onset and triggering a variety of "closed-loop" therapies, such as cortical stimulation, focal drug perfusion, or cooling.

References

1. Roy C, Sherrington C. On the regulation of the blood supply to the brain. *J Physiol* 1890;11:85–108.
2. Fox PT, Raichle ME, Mintun MA, Dence C. Nonoxidative glucose consumption during focal physiologic neural activity. *Science* 1988;241:462–464.
3. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 1990;87:9868–9872.

4. Frostig RD, Lieke EE, Ts'o DY, Grinvald A. Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by in vivo high-resolution optical imaging of intrinsic signals. *Proc Natl Acad Sci* 1990;87:6082–6086.
5. Malonek D, Grinvald A. Interactions between electrical activity and cortical microcirculation revealed by imaging spectroscopy: implications for functional brain mapping. *Science* 1996;272:551–554.
6. Mayhew JEW, Zheng Y, Hou Y, Vuksanovic B, Berwick J, Askew S, Coffey P. Spectroscopic analysis of changes in remitted illumination: the response to increased neural activity in brain. *Neuroimage* 1999;10:304–326.
7. Vanzetta I, Grinvald A. Increased cortical oxidative metabolism due to sensory stimulation: implications for functional brain imaging. *Science* 1999;286:1555–1558.
8. Thompson JK, Peterson MR, Freeman RD. Single-neuron activity and tissue oxygenation in the cerebral cortex. *Science* 2003;299:1070–1072.
9. Ances BM, Buerk DG, Greenberg JH, Detre JA. Temporal dynamics of the partial pressure of brain tissue oxygen during functional forepaw stimulation in rats. *Neurosci Lett* 2001;306:106–110.
10. Logothetis NK, Gugenberger H, Peled S, Pauls J. Functional imaging of the monkey brain. *Nature Neurosci* 1999;2:555–562.
11. Kim D-S, Duong TQ, Kim S-G. High-resolution mapping of iso-orientation columns by fMRI. *Nature Neurosci* 2000;3:164–169.
12. Sheth SA, Nemoto M, Guiou G, Walker M, Pouratian N, Toga AW. Linear and nonlinear relationships between neuronal activity, oxygen metabolism, and hemodynamic response. *Neuron* 2004;42:347–355.
13. Lindauer U, Royl G, Leithner C, Kuhl M, Gold L, Gethmann J, Kohl-Bareis M, Villringer A, Dirnagl U. No evidence for early decrease in blood oxygenation in rat whisker cortex in response to functional activation. *Neuroimage* 2001;13:988–1001.
14. Folbergrova J, Ingvar M, Siesjo BK. Metabolic changes in cerebral cortex, hippocampus, and cerebellum during sustained bicuculline-induced seizures. *J Neurochem* 1981;37:1228–1238.
15. Simon RP. Physiologic consequences of status epilepticus. *Epilepsia* 1985;26(suppl 1):S58–S66.
16. Meldrum BS. Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. *Prog Brain Res* 2002;135:3–11.
17. Plum F, Posner JB, Troy B. Cerebral metabolic and circulatory responses to induced convusions in animals. *Arch Neurol* 1968;18:1–13.
18. Ingvar M. Cerebral blood flow and metabolic rate during seizures. Relationship to epileptic brain damage. *Ann N Y Acad Sci* 1986;462:207–223.
19. Horton RW, Meldrum BS, Pedley TA, McWilliam JR. Regional cerebral blood flow in the rat during prolonged seizure activity. *Brain Res* 1980;192:399–412.
20. Tanaka S, Sako K, Tanaka T, Nishihara I, Yonemasu Y. Uncoupling of local blood flow and metabolism in the hippocampal CA3 kainic acid-induced limbic seizure status. *Neuroscience* 1990;36:339–348.
21. Siesjo BK, Wieloch T. Epileptic brain damage: pathophysiology and neurochemical pathology. *Adv Neurol* 1986;44:813–847.
22. Pinard E, Tremblay E, Ben-Ari Y, Seylaz J. Blood flow compensates oxygen demand in the vulnerable CA3 region of the hippocampus during kainate-induced seizures. *Neuroscience* 1984;13:1039–1049.
23. Jobsis FF, O'Connor M, Vitale A, Vreman H. Intracellular redox changes in functioning cerebral cortex. I. Metabolic efects of epileptiform activity. *J Neurophysiol* 1971;34:735–741.
24. Mayevsky A, Chance B. Metabolic responses of the awake cerebral cortex to anoxia, hypoxia, spreading depression and epileptiform activity. *Brain Res* 1975;98:149–165.
25. Kreisman NR, Rosenthal M, LaManna JC, Sick TJ. Cerebral oxygenation during recurrent seizures. *Adv Neurol* 1983;34:231–239.
26. Kreisman NR, Sick TJ, Rosenthal M. Concepts of brain oxygen sufficiency during seizures. *Adv Exp Med Biol* 1984;180:381–392.
27. Pereira de Vasconcelos A, Ferrandon A, Nehlig A. Local cerebral blood flow during lithium-pilocarpine seizures in the developing and adult rat: role of coupling between blood flow and metabolism in the genesis of neuronal damage. *J Cereb Blood Flow Metab* 2002;22:196–205.
28. Kreisman NR, Magee JC, Brizzee BL. Relative hypoperfusion in rat cerebral cortex during recurrent seizures. *J Cereb Blood Flow Metab* 1991;11:77–87.
29. Tenney JR, Duong TQ, King JA, Ferris CF. FMRI of brain activation in genetic rat model of absence seizures. *Epilepsia* 2004;45:576–582.
30. Nersesyan H, Hydeer F, Rothman DL, Blumenfeld H. Dynamic fMRI and EEG recording during spike-wave seizures and generalized tonic-clonic seizures in WAG/Rij rats. *J Cereb Blood Flow Metab* 2004;24:589–599.
31. Benar CG, Gross DW, Wang Y, Petre V, Pike B, Dubeau F, Gotman J. The BOLD response to interictal epileptiform discharges. *Neuroimage* 2002;17:1182–1192.
32. Krakow K, Messina D, Lemieux L, Duncan JS, Fish DR. Functional MRI activation of individual interictal epileptiform spikes. *Neuroimage* 2001;13:502–505.
33. Jager L, Werhahn KJ, Hoffmann A, Berthold S, Scholz V, Weber J, Noachtar S, Reiser M. Focal epileptiform activity in the brain: detection with spike-related functional MR imaging—preliminary results. *Radiology* 2002;223:860–869.
34. Aghakhani Y, Bagshaw AP, Benar CG, Hawco C, Andermann F, Dubeau F, Gotman J. fMRI activation during spike and wave discharges in idiopathic generalized epilepsy. *Brain* 2003;127:1127–1144.
35. Salek-Haddadi A, Diehl B, Hamandi K, Merschhemke M, Liston A, Friston K, Duncan JS, Fish DR, Lemieux L. Hemodynamic correlates of epileptiform discharges: an EEG-fMRI study of 63 patients with focal epilepsy. *Brain Res* 2006;1088:148–166.
36. Salek-Haddadi A, Merschhemke M, Lemieux L, Fish DR. Simultaneous EEG-Correlated Ictal fMRI. *Neuroimage* 2002;16:32–40.
37. Detre JA, Sirven JI, Alsop DC, O'Connor MJ, French JA. Localization of subclinical ictal activity by functional magnetic resonance imaging: correlation with invasive monitoring. *Ann Neurol* 1995;38:618–624.
38. Schwartz TH, Resor SR Jr., De La Paz R, Goodman RR. Functional magnetic resonance imaging localization of ictal onset to a dysplastic cleft with simultaneous sensorimotor mapping: intraoperative electrophysiological confirmation and postoperative

follow-up: technical note. *Neurosurgery* 1998;43:639–644; discussion 644-635.
39. Bahar S, Suh M, Zhao M, Schwartz TH. Intrinsic optical signal imaging of neocortical seizures: the "epileptic dip." *Neuroreport* 2006;17:499–503.
40. Shariff S, Suh M, Zhao M, Ma H, Schwartz TH. Recent developments in oximetry and perfusion-based mapping techniques and their role in the surgical treatment of neocortical epilepsy. *Epilepsy Behav* 2006;8:363–375.
41. Suh M, Shariff S, Bahar S, Mehta AD, Schwartz TH. Intrinsic optical signal imaging of normal and abnormal physiology in animals and humans—seeing the invisible. *Clin Neurosurg* 2005;52:135–149.
42. Suh M, Bahar S, Mehta AD, Schwartz TH. Temporal dependence in uncoupling of blood volume and oxygenation during interictal epileptiform events in rat neocortex. *J Neuroscience* 2005;25:68–77.
43. Dymond AM, Crandall PH. Oxygen availability and blood flow in the temporal lobes during spontaneous epileptic seizures in man. *Brain Res* 1976;102:191–196.
44. Cooper R, Crow HJ, Walter WG, Winter AL. Regional control of cerebral vascular reactivity and oxygen supply in man. *Brain Res* 1966;3:174–191.
45. Adelson PD, Nemoto E, Scheuer M, Painter M, Morgan J, Yonas H. Noninvasive continuous monitoring of cerebral oxygenation periictally using near infrared spectroscopy: a preliminary report. *Epilepsia* 1999;40:1484–1489.
46. Suh M, Zhao M, Ma H, Perry C, Schwartz TH. Increased perfusion and decreased hemoglobin oxygenation predict the onset of spontaneous seizures in human cortex. Presented at Society for Neuroscience, Atlanta, Georgia, October 14–18, 2006.
47. Schwartz TH, Suh M, Bahar S, Mehta AD, Ma H, Zhao M, Shariff S, Wong K. Optical imaging of intrinsic signal during epileptiform afterdischarges in human cortex. Presented at Society for Neuroscience, Washington, DC, November 12–16, 2005.
48. Gibbs FA. Cerebral blood flow preceding and accompanying experimental convulsions. *Arch Neurol Psychiatr Chicago* 1933;30:1003–1010.
49. Weinand ME, Carter LP, Patton DD, Oommen KJ, Labiner DM, Talwar D. Long-term surface cortical cerebral blood flow monitoring in temporal lobe epilepsy. *Neurosurgery* 1994;35:657–664.
50. Diehl B, Knecht S, Deppe M, Young C, Stodieck SR. Cerebral hemodynamic response to generalized spike-wave discharges. *Epilepsia* 1998;39:1284–1289.
51. De Simone R, Silvestrini M, Marciani MG, Curatolo P. Changes in cerebral blood flow velocities during childhood absence seizures. *Pediatr Neurol* 1998;18:132–135.
52. Makiranta M, Ruohonen J, Suominen K, Niinimaki J, Sonkajarvi E, Kiviniemi V, Seppanen T, Alahuhta S, Jantti V, Tervonen O. BOLD signal increase preceeds EEG spike activity–a dynamic penicillin induced focal epilepsy in deep anesthesia. *Neuroimage* 2005;27:715–724.
53. Hoshi Y, Tamura M. Cerebral oxygenation state in chemically induced seizures in the rat—study by near infrared spectrophotometry. *Adv Exp Med Biol* 1992;316:137–142.
54. Chen JWY, O'Farrell AM, Toga AW. Optical intrinsic signal imaging in a rodent seizure model. *Neurology* 2000;55:312–315.
55. Zhao M, Suh M, Ma H, Perry A, Geneslaw A, Schwartz TH. Focal increases in perfusion and decreases in hemoglobin oxygenation precede seizure onset in spontaneous human epilepsy. *Epilepsia* in review.