Imaging preictal hemodynamic changes in neocortical epilepsy

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Object. The ability to predict seizure occurrence is extremely important to trigger abortive therapies and to warn patients and caregivers. Optical imaging of hemodynamic parameters such as blood flow, blood volume, and tissue and hemoglobin oxygenation has already been shown to successfully localize epileptic events with high spatial and temporal resolution. The ability to actually predict seizure occurrence using hemodynamic parameters is less well explored.

Methods. In this article, the authors critically review data from the literature on neocortical epilepsy and optical imaging, and they discuss the preictal hemodynamic changes and their application in neurosurgery.

Results. Recent optical mapping studies have demonstrated preictal hemodynamic changes in both human and animal neocortex.

Conclusions. Optical measurements of blood flow and oxygenation may become increasingly important for predicting and localizing epileptic events. The ability to successfully predict ictal onsets may be useful to trigger closed-loop abortive therapies.

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Hemodynamic signals derived from perfusion and oximetry significantly correlate spatially with brain function. They are the fundamental basis of functional neuroimaging. In recent years, there has been great interest in using a variety of brain mapping techniques that measure those hemodynamic responses to assist in clinical diagnosis and management of neurological disorders. In particular, seizures have been shown to elicit a large increase in metabolism, utilization of oxygen, and increases in blood flow and blood volume in epileptic cortex. More recently, it has become apparent that these hemodynamic changes may actually precede seizure onset and be useful at seizure prediction. In the present report, we review the literature on functional optical imaging methods and explore recent data on the timing and the significance of anticipatory preictal hemodynamic changes and their potential application in neurosurgery.

Abbreviations used in this paper: CBF = cerebral blood flow; CBV = cerebral blood volume; ECoG = electrocorticography; EEG = electroencephalography; fMRI = functional MRI; LFP = local field potential; LVFA = low-voltage fast activity; ORIS = optical imaging of intrinsic signals.

Prediction of Seizure Onset

Epilepsy is a clinical term referring to a disease involving recurrent seizures that affects between 1% and 2% of the population of the United States. Seizures can be sudden and occur without warning, which can cause significant injuries. The possibility of identifying events, whether they are behavioral, electrographic, or hemodynamic, that reliably occur before epileptic seizures would have a dramatic impact on our ability to warn patients and their families of an upcoming event, thereby giving patients the ability to remove themselves from harm’s way. Attempts have been made to forecast epileptic seizures using a variety of methodologies such as EEG,6,12 fMRI,6,12 SPECT,42 among others.50 Such preictal signals could also provide information for “closed-loop” abortive therapies such as cortical stimulation,24 focal drug perfusion,11,45 cooling,7 and optical inhibition.25,49,53 Additionally, seizure prediction mechanisms can offer insights into epileptogenesis.16

Traditional analysis of EEG signals has not shown any obvious or consistent preictal changes.23,34 Complex nonlinear mathematic algorithms for electrographic data can be used to predict seizure with increasing reliabili-
ty. Recently, our laboratory reported an approximately 20-sec focal hemodynamic change before seizure onset in human leisional neocortical case. In addition, we have shown preictal vessel constriction as early as 5 sec prior to seizure onset in an animal model using a 2-photon microscope. Recently, our laboratory reported an approximately 20-sec focal hemodynamic change before seizure onset in human leisional neocortical case. In addition, we have shown preictal vessel constriction as early as 5 sec prior to seizure onset in an animal model using a 2-photon microscope.57,58

**Intrinsic Optical Mapping of Neurovascular Coupling During Epilepsy**

Neurovascular coupling concerns the relationship among neuronal activity, metabolism, tissue oxygenation, and blood flow. Adequate coupling is critical to supply the energy demands of the brain during normal physiological function as well as pathological conditions. Seizures create a large focal increase in metabolism and result in a dramatic increase in CBF to the ictal focus to provide adequate oxygenation. Whether CBF is adequate to meet the demands of an epileptic event has been a longstanding debate.

Optical imaging of intrinsic signals is a technique for measuring hemodynamic changes in the brain and is based on enhanced light absorption of active neural tissue, which is caused by focal increases in CBF, deoxygenation of hemoglobin, and enhanced scattering of light. At wavelengths such as 570 nm, an isosbestic wavelength of hemoglobin, ORIS provides a direct measure of total hemoglobin. Total hemoglobin is equivalent to CBF if the hematocrit remains constant, and CBV is proportional to CBF. At 610 nm, deoxygenated hemoglobin absorbs light more strongly than oxygenated hemoglobin, and it is possible to directly quantify both deoxygenated hemoglobin and total hemoglobin with the appropriate calculation. At 800 nm, or near infrared wavelengths, the optical signal is largely derived from light scattering related to cell swelling as well as intra- and extracellular fluid shifts, which provide an indirect representation of neuronal activity, less influenced by the changes in CBV and hemoglobin oxygenation that dominate the intrinsic signal at lower wavelengths.

Precise localization of neocortical epileptic foci is very important for the neurosurgeon to identify and remove the seizure onset zone to achieve the best surgical outcome. Several studies have shown that ORIS can be used to map the onset and spread of epileptic events via their hemodynamic sequelae with very high spatial and temporal resolution, as well as high spatial sampling.34-40 Epileptic events initiate a large focal increase in metabolism and CBF at the seizure focus. In contrast, decreases in CBF have been demonstrated surrounding the focus, the etiology of which is unknown. The relationship between these events and neuronal activity and metabolism is also unknown. Studies using techniques with limited spatial and temporal resolution such as fMRI, PET, SPECT, and autoradiography have shown that the relative increase in CBV more than the increase in metabolism leading to an increase in blood oxygenation; however, studies using higher temporal resolution techniques such as near-infrared spectroscopy and ORIS have demonstrated that CBF is inadequate to meet the metabolic demands of the epileptic tissue, leading to a decrease in both tissue and hemoglobin oxygenation (see review).40

**Optical Signals and Seizure Prediction**

**Mapping Preictal Changes in Human Epilepsy**

Optical imaging has been intraoperatively done to map both human epileptic focus and human brain function activity during surgery. Beyond localizing human physiological and pathological activity, it was also used to predict the preictal changes in human epilepsy.

The idea of preictal vascular reactivity predicting the seizure onset was proposed (mistakenly at the time) as early as 1933 by Gibbs. More recently, studies have found increases in cerebral perfusion 20 minutes before focal and generalized spike-and-wave events using transcranial Doppler ultrasonography.10 Fortuitously, we recorded ORIS in human cortex intraoperatively in a patient with recurrent focal seizures arising from a cavernous malformation.15 We found that focal changes in cerebrovascular hemodynamics preceded the seizure onset by approximately 20 sec and occurred focally over the known location of the lesion and the seizure onsets (Fig. 1). Three spontaneous seizures were successfully recorded, two at 610 nm and one at 570 nm, providing data on deoxygenated hemoglobin and CBV. Each seizure was accompanied by a dramatic focal change in the intrinsic signal. At 610 nm, a significant increase light reflectance began 23.74 ± 8.67 sec prior to the electrographic onset of the seizure (Fig. 1D and F). The spatial maps of the two seizures recorded at 610 nm were remarkably similar. At 570 nm, a significant decrease in light reflectance began 15.0 sec prior to the electrographic onset of the seizure (Fig. 1E), again restricted to the known epileptic gyrus consistent with a focal drop in CBV. Prior to the onset of the seizures, the signal inverted to a significant increase in light reflectance (increase in CBV), which reached a maximum amplitude of 46.2%, peaking 58.1 sec after the onset of the seizure. Again the signal was restricted to the known epileptic gyrus consistent with a focal drop in CBV. Prior to the onset of the seizures, the signal inverted to a significant increase in light reflectance (increase in CBV), which reached a maximum amplitude of 46.2%, peaking 58.1 sec after the onset of the seizure. This preictal finding in spontaneous human epilepsy suggests that optical measurements may be useful for predicting the seizure onset and location prior to any electrographic changes.

**Optical Imaging of Preictal Changes in an Animal Model**

Despite the discovery of preictal optical signals in human spontaneous epilepsy, many of our animal studies in pharmacologically induced recurrent focal neocortical seizures using 4-aminopyridine injection did not find any preictal changes in intrinsic optical imaging, autofluorescence flavoprotein metabolism, or direct tissue measurements. In another study, however, we divided these 4-aminopyridine seizures into two groups based on their electrographic onset pattern. While some seizures began with a large population spike, followed by LVFA,
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others began with LVFA without an initial spike. Of the 67 seizures, 47 began with an initial spike and 20 began without the initial spike. Using ORIS to record CBV, when an initiating spike occurred, increases were identified 0.653 ± 0.482 sec after the initial spike. However, for the 20 seizures that did not begin with an initial spike but an LVFA recruiting rhythm, CBV increases occurred 1.525 ± 1.218 sec before the first significant change in the LFP. Thus, preictal increases in CBV can depend on pattern of seizure onset (Fig. 2).

Surrounding Vasoconstriction of Preictal Signals

To determine the etiology of the preictal vascular signals, we recently used 2-photon imaging to measure changes in arteriolar diameter during acute 4-aminopyridine–induced seizures and found preictal vasoconstriction in the cortex surrounding an ictal focus. In vivo images of cortical vasculature were used to measure vessel diameter (Fig. 3A). High-magnification movies of individual arterioles allowed for tracking diameter changes during seizure activity near to (Fig. 3B and C) and far from (Fig. 3D and E) the seizure focus (Fig. 3A–E). We found that arterioles dilated in response to the seizure in the focus, with a decreasing amount of dilation with increasing distance from the 4-aminopyridine injection site (n = 4 rats, 71 vessels, 45 seizures, 143 measurements). Plotting the temporal profile of vasodilation compared with vasoconstriction (Fig. 3F and G), we determined that vasodilation in the focus occurred 0.5 ± 0.1 sec after seizure onset, whereas vasoconstriction in the surround occurred 5.3 ± 0.5 sec before seizure onset. Note that all vasoconstriction was observed to occur before seizure onset.

In previous studies, we had demonstrated inverted ORIS in the surround consistent with a decrease in CBV. It was not clear from these studies whether the surrounding decrease in CBF or CBV was caused by a passive shunting of blood into the ictal focus or by active shunting of blood due to vasoconstriction on the surrounding brain tissue. Using the 2-photon microscope to look directly at the arterioles, we demonstrated active preictal vasoconstriction, indicating that ictal onset may be preceded by vasoconstriction in small arterioles surrounding an ictal focus. The etiology of preictal surround vasoconstriction is unclear. One possibility is the active shunting of oxygenated blood to the imminent seizure focus. Another possibility is that the vasoconstriction is a reaction to preictal surround inhibition in the “ictal penumbra.”

Discussion

Preictal optical imaging studies in both human and animal seizures provides converging evidence for the existence of anticipatory changes in CBF and hemoglobin.
oxygenation. Although the etiology of those changes is currently unknown, ORIS can be used as a method to detect these early events. Whether these vascular events are truly preictal or, rather, represent subtle underlying neuronal or glial events is also unclear and will require more sensitive measurements of both signals. For example, fast ripples (very high frequency activity) and microseizures have been recorded in human epilepsy using high-resolution ECoG techniques,6,22,37,43,44 which were not applied in our aforementioned studies. Ictal change in the ECoG or the LFP are a reflection of synchronous dendritic activity in large groups of neurons. In optical imaging, intrinsic signal recordings mostly arise from subthreshold activity in an area 5–10 times larger than the area of spiking cells. Hence, subtle preictal activity may not be recorded by the ECoG or LFP electrode but may be clearly recorded by optical methods. Additionally, preictal signals may not be elicited by neurons but, rather, by astrocyte- or pericycle-mediated signaling or local potassium and local neurotransmitter/neuropeptide release.14,20,21,32,51 Hemodynamic changes may also be influenced by glia, which are not directly recorded with standard electrophysiological methods.

What is the significance of the preictal optical signal?

The ultimate goal of optical seizure prediction is not only to warn of an impending seizure but also to prevent seizure from occurring. New novel epilepsy therapies such as cortical stimulation, local short-acting, powerful drug application, and focal cooling have been investigated to stop seizures.7,11,24,31,45 All of these methodologies would be more efficacious if those closed-loop intervention systems could predict the onset of seizures.

Currently, most of those systems use recording electrodes to provide ongoing feedback of cortical physiology.
Intrinsic optical imaging of seizure onset

The number and location of electrodes may be important to provide a sufficiently early detection of an ongoing seizure. Complex mathematical algorithms applied to electrographic data for seizure prediction have recently garnered much attention. The preictal optical signals we describe here may provide an alternative method. Additionally, the method is a noninvasive measurement that can avoid the brain damage caused by implanted electrodes. New neuroimaging and neuromodulatory techniques such as "optogenetics," which combines optical and genetic techniques, have emerged as popular tools to probe and control neuronal function with light. Recently, optical suppression of epilepsy has been studied by using optogenetic techniques and caged compounds. The combination of optical preictal detection and optical control would make a novel optical device to terminate seizures.

Pretical optical imaging may also help to identify the ictal focus in patients with nonlesional epilepsy. Nonlesional epilepsy surgery usually has a lower chance of seizure-free outcome than lesional epilepsy surgery. Precise location of a preictal and ictal onset zone in presurgical planning would result in more effective neurosurgical resections.

**Conclusions**

In summary, new novel optical imaging techniques show clear preictal optical signals from both epilepsy in humans and acute pharmacologically induced seizures in animal models. Optical measurements of blood flow and oxygenation may be extremely useful tools for predicting and localizing seizure onset, which can have a myriad of uses in warning patients and triggering abortive therapies. Those methods have great potential to assist the neurosurgeon not only in localizing the seizure onset but also in triggering a closed-loop, real-time, online device to predict and terminate seizures.

**Disclosure**

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References
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