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Haemodynamic response associated with both ictal and interictal epileptiform activity using simultaneous video electroencephalography/near infrared spectroscopy in a within-subject study

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Abstract

This paper reports the findings from a pilot study of four patients with medically refractory epilepsy undergoing pre-surgical evaluation with ages ranging from 5 to 17 years. Video electroencephalography recordings and data from a near infrared spectroscopy cerebral/somatic oximeter were gathered and related to electrographic seizure onset and offset as determined by a paediatric epileptologist. All four patients showed haemodynamic changes associated with epileptiform activities. The increased blood flow clearly coincided with epileptiform activity and continued to increase as the epileptiform activity built up. Regional cerebral oxygen saturation increased in the epileptogenic focus, perhaps due to loss of cerebrovascular autoregulation. These findings reinforce that near infrared spectroscopy can potentially be used in a wide spectrum of patients with epilepsy regardless of the underlying brain pathology.

Keywords

epilepsy; seizure; brain oxygen consumption; haemodynamic response; cerebrovascular autoregulation; monitoring oxygen; oxygen saturation; ictal; interictal; electroencephalography; near infrared spectroscopy

Introduction

Near infrared (NIR) spectroscopy is a non-invasive method for continuously measuring regional cerebral oxygenation (SaO₂). This has been used to monitor cerebral oxygenation and blood flow in various conditions including cardiac arrest and perinatal distress.^{1,2}

Simultaneous video electroencephalography (EEG)/NIR spectroscopy recording is an evolving technique used to monitor both electrical and regional haemodynamic changes in

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patients with epilepsy.³ It is well established that sustained changes in neuronal activity produce haemodynamic changes and vice versa.⁴

“The INVOS™ system provides real-time monitoring of changes in regional oxygen saturation (rSO₂) of blood in the brain or other body tissues beneath the sensor for effective oxygen monitoring in adults, children, infants and neonates. Available in two or four data channels, clinicians can conveniently monitor multiple brain and body areas.” (<http://www.covidien.com/rms/products/cerebral-somatic-oximetry/invos-5100c-cerebral-somatic-oximeter>)

NIR signals reflect predominantly the O₂ availability in the microcirculation of underlying tissue with a penetration of approximately 2–6 cm. This can be applied to monitor a variety of tissues including the brain, muscle and connective tissue.⁵

Although it has been over three decades since the technique was first described⁶ and over 20 years after the development of the first commercial monitors,⁷ the clinical applications of NIR spectroscopy still remain limited.⁸

There have not been many studies utilising a within-subject design investigating the NIR spectral changes in patients with epilepsy. Ipsilateral changes in SaO₂ in patients with focal seizures have previously been reported, but there was no comparison with oxygenation changes in the contralateral hemisphere.⁹ In addition, we were able to sample NIR data at 4 Hz, which represents a significant improvement over most reported studies where the machines update readings only every 4 s.

Materials and methods

This study included four patients with medically refractory epilepsy (Table 1) undergoing pre-surgical evaluation with ages ranging from 5 to 17 years. These patients volunteered to participate in this study. Informed consents were obtained from the parents of all subjects. This study was approved by the Medical College of Wisconsin Institutional Review Board.

Data from each patient were analysed separately to evaluate the presence of seizure-related patterns in the NIR reading for each patient. The general statistical approach was linear modelling with within-episode correlation incorporated via random effects for patients 1 and 2. For plotting, spline-based curves over time were fitted to visualise the average trend. Analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Procedures

Video EEG/NIR recordings were carried out as part of the research protocol. Scalp EEG electrodes were placed according to the International 10-20 system.

A commercially available INVOS 5100C cerebral/somatic oximeter (Covidien plc, Mansfield, MA, USA) was used for this study without any modifications. Paediatric probes utilising LED wavelengths of 730 nm and 810 nm were used.

The probes sampled at 15 Hz, and an averaged rSO₂ displayed on the INVOS monitor for clinical purposes was captured. However, the NIR data were directly sampled and integrated into the EEG recording as described below. The past medical and seizure history and EEG findings were used to determine the location for the INVOS probe.

The probe was placed on the ipsilateral side to the epileptogenic lesion, and compared with the probe placed on the contralateral hemisphere for self-control. INVOS probes were applied to the scalp as per the standard protocol and we did not encounter any problem with scalp hair or attachment. Electrographic seizure onset and offset were determined by a paediatric epileptologist. Oxygen saturation data were collected for one minute each in preictal, ictal and postictal periods. Data were similarly collected for multiple seizures in the first two patients. The third patient had a condition known as ESES. So we took 5 samples of one minute each (5 samples while awake and 5 samples while asleep). The fourth patient had no clinical seizures, and hence we took 5 samples (one minute each) randomly with no interictal changes and 5 samples during a period when EEG showed interictal changes.

The NIR data were correlated and time-synchronised with EEG data using the analogue outputs on the INVOS 5100C monitor, from which the signal arises and then passes through a voltage divider to get the signal at the correct level for the Natus EEG system (<http://www.natus.com>).

The Natus EEG system has four analogue inputs for oximetry. Only three analogue inputs for oximetry were utilised to feed the NIR data from the three NIR spectroscopy probes on each patient (two cerebral, one somatic).

Thereafter a montage was created in the EEG software to display the cerebral oximetry simultaneously with the EEG data. The signal was then calibrated using a Covidien NIR calibration box and Natus software tools. The NIR signals were collected in real time and time-synchronised with the EEG collection. The EEG report data show the waveform and numerical data of the NIR signals alongside the EEG signals and events in one single display for analysis.

Results (summarised in Table 1)

The first patient had localisation-related epilepsy with left central focus. The patient was known to have an area of hypometabolism over the left central head regions per standard FDG-PET imaging with corresponding decreased interictal NIR readings representing hypoperfusion.

The second patient had multiple electrographic seizures arising from the left hemisphere. These were all associated with a statistically significant increase in recorded NIR spectral numbers over the left hemisphere starting in the immediate postictal phase followed by a gradual return to baseline.

The third patient had a diagnosis of electrical status epilepticus of slow-wave sleep with nearly continuous left hemispheric epileptiform discharges activated by sleep. This was

associated with sleep-activated hyperperfusion over the left hemisphere despite symmetric perfusion over both hemispheres during wakefulness.

The fourth patient had baseline hyperperfusion on the right side with frequent right hemispheric epileptiform discharges. During periods of frequent discharges there was a further increase in the NIR signal over the right hemisphere, compared with periods of few interictal discharges.

Case studies

Patient 1

A 5-year-old male with autism and refractory localisation-related epilepsy with focal cortical thickening and blurring of grey white matter differentiation in the medial aspect of posterior left superior frontal gyrus.

Interictal positron emission tomography (PET) scan revealed a focal area of hypometabolism along the parafalcine left superior frontal gyrus. This extended down into the left cingulate gyrus corresponding with the area of T2 prolongation seen on magnetic resonance imaging (MRI). Seizures last less than a minute and manifest as fencer-type posturing with right arm extension and head and eyes tonically deviated to the right. The interictal EEG showed phase-reversing sharp waves and spikes over the left centroparietal and occasionally in the left frontal region (Figure 1). Ten electro-clinical seizures were sampled (Figure 2). Note the baseline hypoperfusion on the left side compared to the right, and the increase in NIR spectra numbers in the ictal/postictal states.

Table 2 shows an estimate of the mean (first two rows) or difference between two means (last row). SE is the standard error of that estimate in parentheses. Figure 3 shows the difference in cerebral oxygen saturation between the affected side and the unaffected side over time.

Patient 2

A 5-year-old male with medically refractory focal clonic seizures of the right arm. PET scan showed a hypometabolic area along the left perirolandic region corresponding to the area of electrographic dysfunction. Brain MRI was normal (Table 1).

EEG did show multiple electrographic and clinical seizures. There were phase-reversing spikes and sharp waves with maximal amplitude over C3 and occasional spread to P3 or F3. These discharges occurred in bursts and at times in runs of up to 10–20 s in duration without clinical correlate. The clinical events included right upper extremity elevation and falling to the left, with or without head and eye deviation to the right.

A second documented seizure semiology had an onset characterised by right arm paraesthesia followed by a loss of tone and rapid fall forwards.

The electrographic correlate to these clinical events was brief bursts of paroxysmal fast activity over C3 and P3 (Figure 4) followed by slowing and disorganisation over the left central, frontal and finally posterior quadrant regions (Figure 5). These events lasted less

than 10 s and five electro-clinical events were sampled. Figure 6 shows the difference in cerebral oxygen saturation (affected side minus unaffected side) over time and Table 3 summarises a comparison of the average difference during different states.

Patient 3

A 10-year-old male with refractory symptomatic localisation-related epilepsy secondary to neurodegenerative encephalopathy of unknown aetiology. There was clear sleep activation of epileptiform activity electrographically with near-continuous left frontal and frontal temporal polyspike sharp and slow-wave complexes (Figure 7). The electro-clinical picture is overall consistent with electrical status epilepticus of slow-wave sleep.

His MRI brain was normal. Magnetic resonance spectroscopy with single voxel placed on the left putamen, left centrum semiovale and along the posterior midline bilateral parieto-occipital cortex showed prominent peaks related to the presence of choline, total creatine and N-acetyl aspartate.

Five samples each in sleep and wakeful state were studied. Note baseline hyperperfusion of left hemisphere in sleep in association with sleep state/EEG changes.

Figure 8 shows the difference in cerebral oxygen saturation in sleep (ictal) and awake states and Table 4 shows a comparison of the average difference in oxygen saturation using a mixed model analysis. Significant difference is observed between the sleep and the awake states.

Patient 4

A 17-year-old young man with a history of medically refractory, symptomatic localisation-related epilepsy, static encephalopathy and multiple malformations of cortical development (Table 1). His preadmission events consist of poor behavioural control and staring spells 8–10 times a day. Brain MRI showed a large area of encephalomalacia in the right posterior parietal region and an area of abnormal thickened grey matter apart from low-lying cerebellar tonsils.

EEG recording was suggestive of asymmetry of the background activity with a slower posterior dominant rhythm over the right posterior head region. There is emergence of right temporal, potentially epileptiform, discharges during sleep (Figure 9). Samples of 5 minutes each in the awake and sleep states were reviewed. Significantly, the patient had no electrographic or clinical seizures, but had frequent interictal discharges.

During sleep, there is noted baseline hyperperfusion on the right side with frequent right hemispheric epileptiform discharges. These discharges were correlated with further increase in the NIR signal over the same hemisphere. In this patient, the contralateral hemisphere also showed raised NIR spectral numbers during epileptiform discharges.

Figure 10 shows a plot of difference in cerebral oxygen saturation and Table 5 shows a comparison of the average difference in cerebral oxygen saturation during sleep (with interictal activity) in comparison to awake state (with no interictal activity).

Discussion

In this study, all four patients showed haemodynamic changes associated with epileptiform activities. The increased blood flow clearly coincided with epileptiform activity and continued to increase as the epileptiform activity built up. The highest level was detected during the immediate postictal phase. Ictal focal hyperperfusion has been demonstrated by several studies in the past using single-photon emission computed tomography (SPECT).^{10–12}

Our finding of increased SaO₂ in the postictal period as compared with preictal baseline has been demonstrated by other investigators using the INVOS NIR spectroscopy machine.⁹

Several studies published recently^{13,14} indicate that the increased blood flow around the time of seizure onset may not be adequate to meet the ictal metabolic demand, leading to decreased tissue and haemoglobin oxygenation. A persistence of increased blood flow, when neural activity is suppressed or normalised, may account for the postictal increase in SaO₂ observed in the present study. Ictal and postictal elevation of end tidal CO₂ lasts several minutes¹⁴ and may contribute to increased blood flow in the postictal period. Furthermore, Adelson *et al.*^{15,16} reported increased SaO₂ several hours before the onset of complex partial seizures, a finding not substantiated in our study. In our second patient, the peripheral SaO₂ did not show any systemic hypoxia. However, many investigations showing decreased SaO₂ with seizures did not report peripheral SaO₂.^{16,17} Large-scale studies, preferably with the inclusion of peripheral SaO₂ measurements, are required.

Our last patient in the series showed haemodynamic response with interictal epileptiform discharges as seen in studies with functional NIR spectroscopy combined with EEG.¹⁸ This is in concordance with the findings in studies using linear time invariant model¹⁹ and statistical parametric mapping. A study²⁰ which correlated NIR spectroscopy with pre-surgical evaluation performed using different modalities (SPECT, PET, EEG/fMRI, magnetoencephalography source localisation and ictal EEG/NIR) did show similar outcomes.

Some studies^{14,21} reported that preictal increase in SaO₂ is followed by a decline in SaO₂ values in proximity to seizure onset. We did not observe this in our study.

This may be due to baseline hypoperfusion in our first two patients and relative hyperperfusion in the second two children. However our findings correlated with postictal increase in SaO₂ reported in other studies.

There were no subclinical seizures in our patients. However, some studies (Adelson *et al.*)¹⁶ found decreased SaO₂ during subclinical seizures. Hence further study of NIR spectra during a large number of electrographic seizures is merited.

Conclusions

This study showed haemodynamic response associated with both ictal and interictal epileptiform activity over one hemisphere, compared to the contralateral hemisphere in the

same patients. It is clear that regional cerebral oxygen saturation increases in the epileptogenic focus, perhaps due to loss of cerebrovascular autoregulation.

All four patients had regional oxygen saturation variability during epileptiform activity. Of note, there was increased oxygen saturation with increased epileptiform discharges, not only during actual seizures. All four patients had baseline brain structural abnormalities of different aetiologies, two with hypoperfusion and two with hyperperfusion on PET or SPECT. The end result was that they all had increased perfusion of the epileptogenic brain hemisphere during or after the ictal and epileptiform activity. These findings reinforce that NIR spectroscopy can potentially be used in a wide spectrum of patients with epilepsy regardless of the underlying brain pathology.

This study is limited by the small number of subjects, diverse nature of aetiology and variation in the quantum of data collected for each patient. Perhaps different models of analysis used for each patient might have adversely influenced the outcome. A larger study with a more homogenised subset of patients may be needed in assessing feasibility of using NIR spectroscopy as a non-invasive adjunctive method of detecting seizures or increased epileptiform activity.

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Figure 1.
Focal cortical dysplasia along the parafalcine left superior frontal gyrus with focal hypometabolism in the first patient. Interictal: sharp waves and spikes.

Figure 2.
Patient 1: EEG/NIR spectroscopy. Ictal state: multiple left hemispheric tonic seizures during the recording.

Figure 3. Plot of difference in cerebral oxygen saturation between affected side and unaffected side over time (patient 1). Each grey line represents a separate episode. The thick black curve shows an averaged estimate using a spline fit.

Figure 4.
Left perirolandic region hypometabolism with multiple seizures in the second patient.
Preictal and ictal paroxysmal fast activity at C3–P3.

Figure 5.
Patient 2: EEG/NIR spectroscopy. Postictal state.

Figure 6. Difference in cerebral oxygen saturation (affected side minus unaffected side) over time for the second patient. Each grey line represents a separate episode. The thick black curve shows an averaged estimate using a spline fit.

Figure 7.
Patient 3: electrical status epilepticus during sleep. Note baseline left hemispheric hyperperfusion on NIR spectroscopy.

Figure 8. Difference in cerebral oxygen saturation in sleep (ictal) versus awake state (non-ictal) for patient 3. Each of the grey lines shows a separate sampling period. The thick black curves show an averaged estimate using a spline fit.

Figure 9. Right temporal epileptiform discharges in patient 4 (note interictal activity in the sleep state).

Figure 10.

Plot of difference in cerebral oxygen saturation colour-coded for sleep (blue) versus awake (red) states for patient 4. Each panel represents a different sampling period.

Table 1Clinical and diagnostics information.^a

Age (years)	Seizure type	MRI	PET/MRS	Ictal EEG	NIR spectrometer
5	Localisation related, tonic stiffening of right arm	Focal cortical thickening at left superior frontal gyrus	PET: focal hypometabolism along the parafalcine left superior frontal gyrus	Left posterior quadrant delta intermixed with spikes and spike slow waves	Ictal and interictal relative hypoperfusion on the left hemisphere with increased SaO ₂ in ictal/postictal state
6	Localisation related, tonic clonic type	Normal	PET: hypometabolic area at left perirolandic region	Paroxysmal fast activity at C3, P3 in brief burst	Ictal relative hypoperfusion on left hemisphere with increased SaO ₂ in postictal state
11	ESES, left hemispheric	Normal	MRS: diminished creatinine in the left centrum semiovale	Nearly continuous spikes over the left hemisphere in sleep	Relative sleep-activated hyperperfusion of left hemisphere with increased SaO ₂ in association with sleep-related EEG changes
17	No seizures during the recording	Right parietal cortical malformation (porencephalic cyst)	None	Frequent bursts of right temporal epileptiform discharges	Interictal hyperperfusion on right with additional increase in SaO ₂ correlating with increased epileptiform discharges

^aEEG, electroencephalography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography.

Table 2

Effect of seizures on the difference in cerebral oxygen saturation (affected side minus unaffected side).

	Estimate (SE)	<i>p</i> -value	Overall <i>p</i> -value
Preictal	−17.1 (0.31)		
Ictal versus preictal	0.85 (0.13)	<0.0001	<0.0001
Postictal versus preictal	−1.51 (0.07)	<0.0001	

Table 3

Comparison of average difference during different states using a mixed model analysis with random subject effect in patient 2.

	Estimate (SE)	<i>p</i> -value	Overall <i>p</i> -value
Preictal	−14.1 (1.28)		
Ictal versus preictal	0.80 (0.48)	<0.0926	<0.1065
Postictal versus preictal	−0.20 (0.24)	<0.4183	

Table 4

Comparison of average difference in oxygen saturation using a mixed model analysis with random subject effect for patient 3. Significant difference is observed between sleep versus awake state.

	Estimate (SE)	<i>p</i> -value
Awake	13.4 (0.41)	
Sleep versus awake	−3.63 (0.59)	<0.0001

Table 5

Cerebral oxygen saturation: average difference during sleep (with interictal activity) in comparison to awake state (with no interictal activity) using a mixed model analysis with random subject effect for patient 4. Note that, although clinically obvious, it is not statistically significant.

	Estimate (SE)	<i>p</i> -value
Awake	17.5 (2.90)	
Sleep	−0.90 (4.15)	0.83