Original article

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Near-infrared spectroscopy shows preictal haemodynamic changes in temporal lobe epilepsy

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ABSTRACT – *Aim*. Growing evidence suggests that focal seizures are preceded by haemodynamic changes. Specifically, changes in cerebral blood flow, blood oxygen level-dependent magnetic resonance imaging, and near-infrared spectroscopy measurements of haemoglobin have been observed in the seizure focus and other brain regions many minutes prior to the onset of spontaneous seizures. The purpose of this study was to detect preictal haemodynamic changes using near-infrared spectroscopy, a portable and non-invasive optical technique that measures changes in cerebral haemoglobin. *Methods*. Five subjects with temporal lobe seizures were studied using near-infrared spectroscopy until a seizure was observed, as confirmed by electroencephalography or clinical symptoms. Relative changes in oxy- and deoxyhaemoglobin, total haemoglobin, and blood oxygen saturation were assessed in the anterior frontal lobes between 15 minutes and one minute prior to seizure onset. *Results*. In all subjects, a decrease in oxyhaemoglobin, total haemoglobin, and oxygen saturation was observed in the frontal lobe, ipsilateral to the presumed seizure focus. On the contralateral side, all subjects showed a decrease in relative oxyhaemoglobin content. No consistent change in deoxyhaemoglobin was seen on either side. *Conclusions*. Preictal haemodynamic changes can be detected in the frontal lobes using near-infrared spectroscopy. Our results suggest that a decrease in metabolic rate, and thus neuronal activity, occurs in the ipsilateral frontal lobe prior to the onset of temporal lobe seizures. Extratemporal haemodynamic changes may therefore be an important marker for seizure anticipation.

Key words: temporal lobe epilepsy, focal seizure, cerebral blood flow, near-infrared spectroscopy, seizure anticipation

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One of the most devastating aspects of seizures is their apparent unpredictability (Jacoby *et al*., 2009), often resulting in work and leisure restriction, driving license suspension, and other limitations. In addition, a seizure occurring at an inopportune time could be life threatening. The ability to anticipate impending seizures would have a profound

impact on the quality of life of individuals with focal epilepsy, allowing new treatment methods such as an early-warning system or directed delivery of a therapeutic stimulus. However, the pathophysiological mechanisms underlying the transition into the seizure state remain unclear.

An incomplete but growing body of evidence suggests that focal seizures are preceded by neurophysiological changes minutes to hours before the manifestation of obvious electrographic changes or clinical symptoms. Motivated by the observation that many individuals with epilepsy report prodromal symptoms long before the onset of a seizure (Boylan, 2002), seizures could be anticipated to varying, but modest, degrees of success based on initial linear and non-linear analyses of EEG recordings (Lehnertz *et al.*, 2003).

More recently, in the first functional MRI (fMRI) study of the preictal state, changes were observed in the blood oxygen level-dependent (BOLD) signal near the suspected seizure focus and other areas several minutes prior to seizure onset in three subjects (Federico *et al.*, 2005). In addition, cerebral blood flow (CBF) studies utilising thermal diffusion flowmetry (Weinand *et al.*, 1997) and single-photon emission computed tomography (SPECT) (Baumgartner *et al.*, 1998) demonstrated preictal hyperperfusion in the epileptic temporal lobe up to 12 minutes prior to seizure onset in subjects with temporal lobe epilepsy (TLE). These studies suggest that the transition from the interictal to ictal state may not be as abrupt as previously thought and that changes in haemodynamics may be detectable as a marker of an impending seizure.

Near-infrared spectroscopy (NIRS) is a sensitive, portable, and non-invasive optical technique that provides real-time measurements of changes in tissue chromophore concentrations. In the near-infrared range (700-1,000 nm), absorption is dominated by haemoglobin (Jobsis, 1977). Transmission of light is a function of reflectance, scattering, and absorption. It is assumed that reflectance and scattering remain constant at a constant wavelength and so changes in absorption are dependent on changes in concentration of the chromophores; largely oxyhaemoglobin (oxyHb) and deoxyhaemoglobin (deoxyHb) (Elwell *et al.*, 1994).

Epileptic events are accompanied by changes in metabolic rate (oxygen extraction) and CBF in the seizure focus (la Fougere *et al.*, 2009). These factors influence haemodynamics, making NIRS an attractive technique for investigating potential preictal changes. To date, NIRS has demonstrated utility in lateralising language dominance in epilepsy patients and controls (Watson *et al.*, 2004), lateralising seizure foci in patients with TLE (Watanabe *et al.*, 2002), and distinguishing between two different seizure types (Sokol *et al.*, 2000). To our knowledge, however, no studies investigating preictal haemodynamic changes have been performed using NIRS. In the present study, five subjects with TLE were monitored continuously with NIRS until they had a seizure. Data were compared in frontal lobes between 15 minutes and one minute prior to seizure onset.

Materials and methods

Five subjects (one female; mean age: 35.4 years; range: 27-48 years) with frequent temporal lobe seizures were recruited from the Comprehensive Epilepsy Program at the Foothills Medical Centre in Calgary, Canada. All subjects were recruited while they were undergoing scalp video-EEG monitoring (VEM) as part of their routine clinical investigations. Subjects were identified as potential candidates based on: 1) focal seizures originating from a single temporal lobe, confirmed by VEM; 2) frequent, daily seizures while undergoing VEM; and 3) an age of at least 16 years old. The only exclusion criterion was previous epilepsy surgery. Subjects had their anticonvulsant dosages reduced during their hospital stay to increase the likelihood of a seizure as part of their presurgical evaluation. This had the added benefit of making a seizure more likely during an NIRS study. Approval was obtained from the University of Calgary Office of Biomedical Ethics and all subjects provided informed consent.

Subjects were monitored continuously with NIRS for one day while undergoing VEM in the Seizure Monitoring Unit of the Foothills Medical Centre. Scalp EEG electrodes were placed according to the international 10-20 system. NIRS data were acquired using a two-channel Hamamatsu NIRO-200 near-infrared oximeter (Hamamatsu Photonics, Hamamatsu City, Japan). Two optodes, consisting each of one emitter and two receivers encased within a rubber housing, were placed over the subjects' forehead, one above each eyebrow. The distances from the emitter to the two receivers were 3.5 and 4 cm, respectively. Care was taken to avoid the frontal sinuses as fluid-filled cavities interfere with the NIRS signal. Optodes were affixed to the skin with NIRS-compatible, double-sided tape and held in place with an elastic headband. Rooms were made as dark as possible by turning off lights and closing window shades to minimise potential interference from external light sources. Subjects were permitted to sleep or remain awake during the study, but were required to remain in their room. The NIRO system was connected to a PC laptop computer during the study *via* a USB cable, during which a manufacturer-designed software program analysed and recorded the data in real time. Data were collected at a rate of 2 Hz.

The NIRO-200 uses three wavelengths of light (775, 810, and 850 nm) and two emitter/receiver distances to calculate relative changes in haemoglobin concentration. Depth and length of light penetration increases with emitter/receiver distance; these distances provide optimal coverage of cerebral cortex, given an average frontal bone thickness of 7.2 mm (Arntsen *et al*., 2008). A modified Beer-Lambert Law was utilised to calculate changes in the concentrations (in μM) of oxygenated and deoxygenated haemoglobin (oxyHb and deoxyHb, respectively) from the initial value, which was designated as 0 μM (Elwell *et al*., 1994). The Spatially Resolved Spectroscopy method was utilised to calculate tissue oxygenation index, TOI (oxygen saturation; the ratio of oxygenated to total haemoglobin) (Wong *et al*., 2009), and normalised tissue haemoglobin index, nTHI (a measure of total haemoglobin; the ratio of the current to the initial value of total haemoglobin) (Myers *et al*., 2009).

Studies were terminated upon the onset of a seizure or if the subject decided to end the study for any reason. Times on the EEG and NIRO systems were manually synchronised and were accurate to within one second. For each subject, seizure onset time was identified based on the first detectable EEG change or clinical symptom; whichever came first as determined by an expert electroencephalographer (PF). The NIRO collects data relative to the first collected point. As data collection was initiated at different times before subjects' seizures, NIRO data were standardised between subjects by normalising with respect to the mean of the minute of data beginning 30 minutes prior to seizure onset. Subsequent values were expressed as changes in μM for oxyHb and deoxyHb, and as percent change for TOI and nTHI. In order to assess changes in the preictal state, one minute of data (from -14 to -15 minutes) was compared with the one minute of data collected immediately prior to seizure onset.

For the statistical analysis, each subject was analysed independently. Values for each parameter were compared between 15 minutes and one minute prior to seizure onset using a two-way analysis of variance (ANOVA) with 120 data points comprising both time points. Significance was defined as $p<0.05$. In addition, the direction of change of each parameter between these times was compared using a non-parametric sign test. All five subjects would need to change in the same direction in order for this to be significant at $\alpha=0.05$.

Results

Patient demographic and clinical information is summarised in *table 1*. All seizures were associated with simultaneous clinical and EEG changes. The recorded seizure foci are listed in *table 1* and were consistent with their overall electro-clinical diagnosis. In addition, Subjects 3 and 5 underwent a left and right temporal lobe resection, respectively, and are currently free of epileptic seizures. Subjects 1 and 4 did not undergo further investigations or surgery. Subject 2 underwent intracranial video-EEG monitoring that suggested that his seizure focus was in the right peri-central region with temporal lobe involvement.

Figure 1 shows the time course of all four NIRS parameters, ipsilateral to the presumed seizure focus for Subject 1 in averaged and normalised one-minute blocks over the 30-minute preictal period. Also shown are the final 60 seconds of normalised, but unaveraged, data to show an example of the variability in the signal immediately prior to seizure onset. Between 14-15 minutes and 0-1 minute prior to seizure onset, an increase in deoxyhaemoglobin was observed, while decreases in oxyhaemoglobin, nTHI, and TOI were observed. Similar changes in oxyHb, nTHI, and TOI were observed in the other four subjects, which are summarised in *figure 2*.

Figure 2 shows the changes between 14-15 minutes and 0-1 minute prior to seizure onset for all NIRS parameters in all five subjects on both sides of the brain.

Table 1. Demographic and clinical information of the five subjects studied.

Subject	Gender	Age	Seizure onset	MRI	Diagnosis
1	Male	30	Left temporal	Left temporal gliosis, left frontal cystic lesion	SGE with CPS
2	Male	27	Right centrotemporal	Unremarkable	Right centrotemporal seizures
3	Female	37	Right temporal	Right anterior temporal cortical dysplasia	Right temporal lobe epilepsy
4	Male	35	Right temporal	Right posterior STG cortical dysplasia	Right temporal lobe epilepsy
5	Male	48	Right temporal	Left temporal hippocampal sclerosis	Bitemporal epilepsy

SGE: symptomatic generalised epilepsy; CPS: complex partial seizures; STG: superior temporal gyrus.

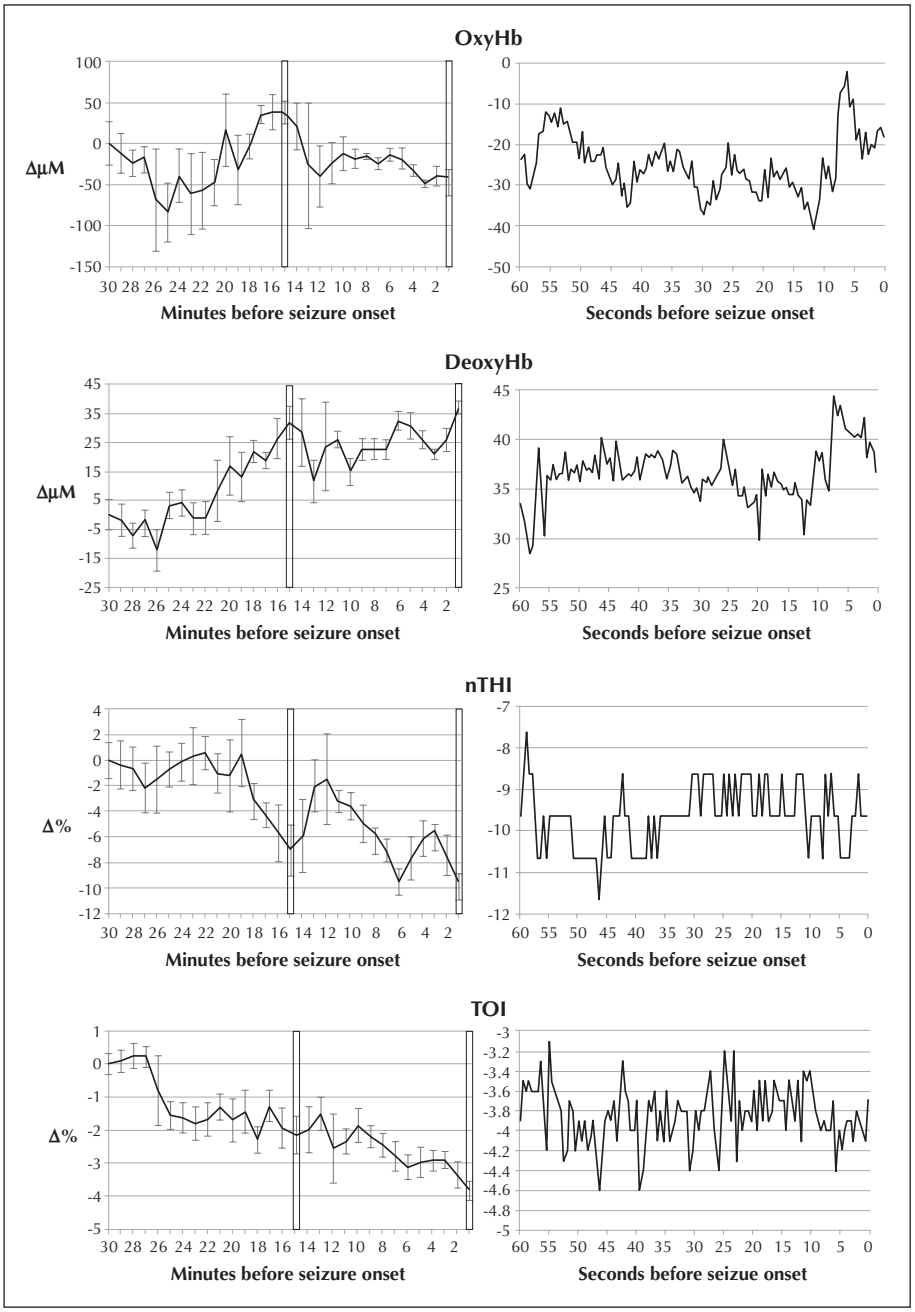

Figure 1. Changes in all four NIRS parameters for Subject 1 on the side ipsilateral to the seizure focus. The left side shows the 30 minutes prior to seizure onset, with each point representing one minute of data (120 data points). Vertical bars at 15 and one minute prior to seizure indicate times used for statistical analysis. We used the one-minute averages for statistics in order to average out the high degree of variability seen in an individual trace. The right side shows unaveraged data for the final minute before seizure onset. Data is shown as mean±SD.

Two-way ANOVAs were undertaken on data from each subject and showed highly significant changes in haemodynamics. Every parameter was significantly different ($p<0.001$) between the two time points. There was no significant difference between the sides of the brain. This shows that with such data sets, it is relatively simple to identify significant changes between these two time points. Of note, review of the EEG showed no state changes, no evidence of seizure activity, or any notable changes in background activity.

In order to gain confidence that this is biologically significant, one can look at the direction of change between these two times. Using a non-parametric sign test, the probability of five subjects changing in the

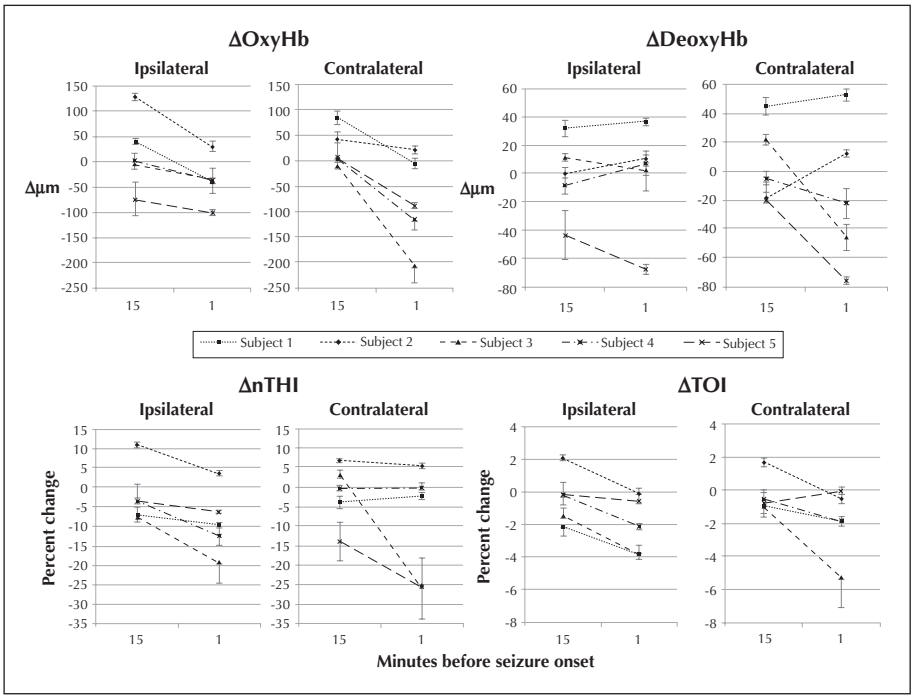

Figure 2. Normalised changes in oxyhaemoglobin (oxyHb), deoxyhaemoglobin (deoxyHb), normalised tissue haemoglobin index (nTHI, an indicator of total haemoglobin), and tissue oxygen index (TOI, an indicator of haemoglobin saturation) between 14-15 minutes and 0-1 minute prior to seizure onset for all five subjects. Data is shown as mean±SD with 120 data points; error bars are shown as only positive or negative in some cases to reduce visual clutter.

same direction if the changes were random would be p=0.031. In all subjects, on the ipsilateral side to the putative seizure focus, there was a decline in oxyHb, nTHI, and TOI between 14-15 minutes and 0-1 minute prior to seizure onset (p<0.05). DeoxyHb showed more variability in the direction of change, with an increase in relative deoxyHb content in three subjects and decrease in two (p>0.05). On the contralateral side, there was a decline in oxyHb in all subjects (p<0.05). DeoxyHb again showed the most variability in the direction of change, with an increase for two subjects and decrease for three subjects. For one subject, there was an increase and four subjects a decrease each in TOI and nTHI on the contralateral side (p>0.05). When we compared the data at -30 minutes to -15 minutes, there was no significant trend in direction of change for any of the parameters.

The last 20 seconds before seizure onset has previously been analysed (Zhao *et al*., 2007). As a comparison, we averaged from -20 to -15 seconds and -5 to 0 seconds before seizure onset. OxyHb increased in all five subjects on the ipsilateral side between these times (p<0.05). Only three subjects showed an increase on the contralateral side (p>0.05). Mixed changes were also observed for deoxyHb (an increase in three and decrease in two), nTHI (an increase in three and decrease in two), and TOI (an increase in two and decrease in three) on the ipsilateral side (p>0.05). *Figure 1* (right side) shows these values for one individual.

Discussion

This study shows that there may be significant changes in haemodynamics beginning at least 15 minutes prior to a seizure. A key factor in the interpretation of haemodynamic data is the concept of neurovascular coupling (Villringer, 1997; Buxton *et al*., 2004), whereby activation leads to an increase in CBF and also an increase in haemoglobin saturation. In the brain, there is also a non-linear relationship between CBF and cerebral blood volume, described by the "Grubb" equation (Grubb *et al*., 1974), where volume increases with CBF. As total haemoglobin can be used as a marker of CBF, it follows that an increase in CBF will be detected as an increase in total haemoglobin (Leung *et al*., 2009), with an implication that there is an increase in metabolic rate.

Preictal changes in CBF and haemodynamics have been previously reported in patients. Using fMRI, it was noted that changes in the BOLD signal occurred over 10 minutes before seizure onset (Federico *et al*., 2005). In addition, SPECT and thermal blood flow

studies described localised preictal changes in CBF up to 12 minutes prior to seizure onset (Weinand *et al*., 1997; Baumgartner *et al*., 1998). This suggests that there may be a window of many minutes to detect haemodynamic changes associated with seizure onset. These data led us to choose the fifteenth minute pre-ictus for comparison with the minute immediately prior to seizure onset in order to determine if there was a significant change in haemodynamics, beginning minutes before the seizure. The choice of time frame for comparison is strengthened by the observation that there was no significant change in parameters when comparing -30 minutes with -15 minutes, relative to seizure onset. Future work will be needed to clarify the time course of change.

The observed decline in total haemoglobin (as measured by nTHI) on the ipsilateral side would indicate that there is a reduction in CBF (Leung *et al*., 2009). If there was normal neurovascular coupling, this decrease in CBF would reflect decreased neuronal activity in the frontal lobes prior to seizure onset. However, the assumption that there is normal neurovascular coupling in the epileptic brain may not hold under all conditions even though there is currently no conclusive evidence to indicate abnormal neurovascular coupling in the preictal state. Although not directly addressing this matter, it has been reported that ictal perfusion is both adequate to meet metabolic demands (Nersesyan *et al*., 2004) and inadequate, resulting in hypoxic injury to neurons (Tanaka *et al*., 1990). There is no conclusive evidence to indicate abnormal neurovascular coupling in the preictal state. A preictal hypometabolic state is also supported by the observed preictal decrease in oxyHb and TOI prior to seizure onset. A deactivation or reduction in metabolic rate in the brain is associated with a decline in tissue oxygenation, at which point haemoglobin saturation declines (Zhu *et al*., 1998; Buxton *et al*., 2004; Young *et al*., 2011), as does the tissue partial pressure of oxygen.

Our observations made during the preictal period are consistent with other studies that have shown ictal and interictal metabolic changes in the frontal lobes in patients with TLE. In addition to interictal temporal hypometabolism, which is well-documented (Engel *et al*., 1982), interictal frontal hypometabolism measured by PET was observed ipsilateral to the epileptic temporal lobe in 31 of 64 (48%) patients with refractory mesial TLE (Wong *et al*., 2010). Ictal SPECT studies of temporal lobe seizures have also demonstrated frontal hypoperfusion in several instances (Rabinowicz *et al*., 1997; Menzel *et al*., 1998; Van Paesschen *et al*., 2003; Dupont *et al*., 2009). Although we are not measuring in the suspected seizure focus, we are hypothesizing that concurrent changes may occur in the frontal lobes due to frontotemporal connectivity via the uncinate or arcuate fasciculi (Kier *et al*., 2004; Glasser and Rilling, 2008). The data in this paper do not indicate whether changes would occur globally throughout the brain.

Haemodynamic changes over different time periods have been previously reported. An NIRS study showed preictal changes in three different patients with unlocalised seizure foci, starting 1, 2 and over 10 hours before seizure onset (Adelson *et al*., 1999). This study also reported the opposite change in oxyHb to that which we observed. The limited numbers, potential differences in seizure focus location, and the variation in time course make this study difficult to compare to ours. In a different study showing data from the few seconds before seizure onset, a decrease in haemoglobin oxygenation in exposed human cortex close to the seizure focus (as confirmed by EEG) was reported to begin about 20 seconds prior to seizure onset (Zhao *et al*., 2007). Our data also showed a change in oxyHb in the final 20 seconds, but cortical oxygenation increased rather than decreased. The fact that haemodynamic changes preceded seizure onset in both cases is important. The differences in direction of the changes could be caused by differences in seizure focus location, differences in location of the NIRS probes relative to the focus, and differences in technique (including the fact that Zhao *et al*. used lower wavelengths).

It has been suggested that interhemispheric inhibition *via* callosal projections may explain the decline in oxygenation seen in the contralateral frontal lobe. Federico *et al*. explored the idea of interhemispheric inhibition as a possible seizure cessation mechanism in their fMRI study of the preictal state (Federico *et al*., 2005). In one subject, widespread BOLD increases were seen in the contralateral hemisphere to the presumed seizure focus and a highly localised BOLD decrease was seen near the focus itself. The authors suggested that this pattern may have reflected an increase in synaptic activity in areas with contralateral inhibitory connections with the seizure focus and that this inhibition may have reflected an attempt by the contralateral region to prevent genesis of a seizure. The BOLD decrease near the seizure focus appears to support this hypothesis. The fact that we have detected haemodynamic changes at sites distant and contralateral to the seizure focus support this concept, highlighting the presence of widespread communication, both intra- and inter-hemispheric, across the brain. The precise nature of this communication is not completely understood.

Our study has some limitations. The regulation of breathing must remain constant, as hyperventilation can reduce blood CO_2 which would result in a decline in CBF (Poulin *et al*., 2002), and factors such as hypoventilation could reduce systemic haemoglobin saturation. Through review of video and clinical

reports, no abnormal changes in breathing were noted during the preictal period in our subjects. Thus, it is unlikely that ventilatory factors were the cause of these preictal changes. Furthermore, the study has limited power as only five subjects were studied. The conclusions thus warrant further investigation with a larger patient cohort. The analyses were also performed under the assumption that 30 minutes prior to seizure onset is a suitable baseline from which to normalise subjects. The fact that prodromal symptoms are often reported long before seizure onset (Boylan, 2002) indicate that haemodynamic changes in some individuals could occur prior to 30 minutes before the seizure.

Conclusion

In the present study, haemodynamic changes were observed in the frontal lobes up to 15 minutes before the onset of temporal lobe seizures. These data are consistent with decreased frontal lobe neuronal activity. Thus, NIRS may be useful for the prediction of seizure onset by detecting haemodynamic changes distant to the seizure focus in subjects with TLE. □

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Authors have no conflict of interest to declare.

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