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Frontal hemodynamic changes precede EEG onset of temporal lobe seizures

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HIGHLIGHTS

- We examined whether preictal hemodynamic changes could be detected non-invasively.
- Near-infrared spectroscopy was used to record hemodynamic changes over frontal scalp in temporal lobe seizures captured during video-EEG telemetry.
- Hemodynamic changes preceded electrographic and clinical seizure onset.

ABSTRACT

Objective: A preictal state exists minutes or hours prior to the clinical seizure. We investigated whether hemodynamic changes preceding temporal lobe seizures were detectable in frontal scalp recordings using near-infrared spectroscopy (NIRS). Patients undergoing video-EEG telemetry (VET) were studied.
Methods: A NIRS sensor was placed over the frontal scalp ipsilateral to the patient's first recorded seizure. Regional cerebral oxygenation (rSO2) was recorded synchronously with VET data and peripheral oxygen saturation (SaO2). Periictal changes in rSO2 were compared with baseline interictal rSO2.
Results: Eleven seizures were recorded in six patients. A mean peak preictal increase in rSO2 of 7.1% from the interictal baseline ($p < 0.001$) occurred at a mean peak latency of 298.9 s before seizure onset. rSO2 then decreased around seizure onset. SaO2 nadir occurred at a mean latency of 62 s following rSO2 nadir. A postictal increase in rSO2 occurred with a mean duration of about 35 min. Periictal rSO2 changes occurred with both ipsi and contralateral temporal lobe seizures.
Conclusion: We have shown that preictal changes in cerebral oxygenation occur with a mean peak latency of about 4.98 min before seizure onset.
Significance: NIRS has the potential for providing a noninvasively detected signal of an imminent seizure.

1. Introduction

Epilepsy is one of the more common serious neurological disorders after stroke with a prevalence of around 1% (Devinsky, 2004). In about 30% of patients with epileptic seizures, remission is unusual and seizures persist despite currently available therapies (Sander, 2003). The unpredictability of seizures is one of the most disabling aspects of this disorder. For patients with persistent uncontrolled seizures, this unpredictability puts the patient at risk for serious injury. A reliable method for alerting a patient that a seizure is imminent would provide a degree of control to the patient. Detection of a preictal state may also be used to administer fast acting antiepileptic drugs or other therapies to prevent clinical seizure onset.

There is evidence indicating a preictal state that may be detected several minutes or hours before the onset of a clinical seizure. Increased neural activity and consequent increases in metabolic demand result in hemodynamic changes (Logothetis et al., 2001; Schwartz et al., 2011). The preictal state is characterized by changes in cerebral blood flow and oxygenation occurring several minutes before clinical and electroencephalographic (EEG) evidence of a seizure (Adelson et al., 1999; Baumgartner et al., 1998, Weinand et al., 1997). In three patients functional MRI (fMRI) analysis in the immediate preictal period showed a regional increase in the blood oxygen dependent (BOLD) signal both ipsilateral and contralateral to the presumed seizure focus (Federico et al., 2005a). In 2 patients SPECT scans obtained fortuitously in the immediate preictal period (11 and 12 min before seizure onset) showed a significant increase in regional blood flow without detectable EEG change during that time (Baumgartner et al., 1998). In direct recordings over the epileptic focus, increases in

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cerebral flow (CBF) relative to baseline were observed in patients with temporal lobe epilepsy starting approximately 20 min prior to clinical seizure onset (Weinand et al., 1994). Transcranial magnetic pulse stimulation showed increased cortical excitability in a 24 h window prior to seizure onset (Badawy et al., 2009). Mathematical and statistical analysis of EEG signals may eventually result in reliable seizure prediction. However, none of the EEG techniques used to date have been shown to reliably predict seizures in prospective studies (Mormann et al., 2007).

Wavelengths used in near-infrared spectroscopy (NIRS) have the ability to penetrate scalp, skull and dura and provide a measure of cerebral oxygen saturation and blood flow (Murkin and Arango, 2009). NIR wavelengths of 700–1300 nm are able to penetrate tissues to a depth of several centimeters (Murkin and Arango, 2009). NIR light is absorbed by metal complex chromophores including hemoglobin, bilirubin and cytochrome (Murkin and Arango, 2009). NIR photons traverse an elliptical pathway between the transmitter and receiver when placed on the scalp with the depth of tissue penetration proportional to the separation of the optodes (Germon et al., 1999). A 5 cm separation of transmitter and receiver allows an NIR penetration of about 1.7 cm giving increased weighting to cerebral rather than extracerebral tissue measures (Ohmae et al., 2006). Closer placement of the optodes monitors signals from primarily superficial extracerebral tissues. This differential effect has been used to distinguish cerebral from extracerebral signals. In order to minimize signal loss by hair and other melanin containing tissues, the transmitter and receiver are placed over the frontal scalp just below the hairline.

Cerebral oximetry studies using NIRS have provided clinically useful information in several settings. Measurements of cerebral oximetry in coronary artery bypass surgery have shown correlations between cerebral oxygen desaturation and outcome (Prabhune et al., 2002). Cerebral oximetry studies have also provided clinically useful information in deep hypothermic circulatory arrest and during cross clamping of the internal carotid artery during carotid endarterectomy (Calderon-Arnulphi et al., 2007; Edmonds et al., 2004).

It is not known whether a preictal change in cerebral oxygenation can be measured non-invasively in patients with temporal lobe epilepsy. We proposed that the immediate preictal change in cerebral oxygenation would be measureable non-invasively with NIRS sensors placed on the scalp. The study sought to determine whether a change in regional cerebral oxygenation (rSO2) occurred predictably prior to seizure onset. Seizure-related changes in peripheral oxygen saturation (SaO2) and end-tidal CO2 (ETCO2) occur and the time course and magnitude of these changes have been determined (Bateman et al., 2008; Seyal et al., 2010). Seizure-related changes in SaO2 and ETCO2 could influence cerebral hemodynamics and we therefore concurrently recorded SaO2 and ETCO2 in all subjects during inpatient video-EEG telemetry (VET). The study was approved by the local Institutional Review Board.

2. Methods

Informed consent was obtained in patients in the epilepsy monitoring unit (EMU) undergoing VET for seizure localization as part of their pre-surgical workup. Following capture of the patient's first seizure, a commercially available NIRS device, Nonin EQUANOX Model 7600 cerebral oximeter (Nonin, Plymouth, MN, USA), was used to record regional cerebral oxygenation (rSO2) data synchronously with the VET data. The cerebral oximeter updates rSO2 values every 4 s and uses light absorption measurements at 3 wavelengths (730, 810 and 880 nm) to estimate rSO2. The oximeter sensor has two emitters and two detectors with 20 and 40 mm spacing. The differential spacing allows subtraction of the extracranial oxygen saturation component and isolates the regional cerebral oxygen saturation component (MacLeod et al., 2012). The sensor pad incorporating the optodes was placed over the frontal scalp, just below the hairline, ipsilateral to the patient's first recorded seizure. The oximeter sensor pad is attached to the scalp with an adhesive layer in the pad. In order to minimize artifact related to movement or from ambient light sources, the edges of the sensor pad were also secured to the scalp with gauze and collodion and the head further wrapped with multiple layers of gauze covering the EEG electrodes and the optode sensor pad. The rSO2 trend data from subsequent seizures was exported and stored on a computer for subsequent analysis. Standard VET recordings in this EMU include synchronized recording of peripheral SaO2 with digital pulse oximetry and ETCO2. The methodology for recording SaO2 and ETCO2 have been described previously (Bateman et al., 2008; Seyal et al., 2010). The study was restricted to patients undergoing standard scalp EEG recordings including T1 and T2 and bilateral mandibular notch electrodes. Oxygen desaturation was defined as a drop in SaO2 below 90% (Bateman et al., 2008).

Baseline rSO2 was defined as the average rSO2, over a 10 min interval in the 1 h preceding electrographic seizure onset. The NIRS rSO2 trend data were analyzed for changes from baseline immediately prior to seizure onset, during the seizure, and in the postictal period. The timing of the first electrographic manifestation of the seizure and the timing of the first behavioral change indicating seizure onset were noted. Increases or decreases in rSO2 that exceeded 2.5 s.d. of the baseline mean for at least 12 s were considered significant. The time of the first of 3 or more consecutive rSO2 values that crossed the 2.5 s.d. line, in either direction, was used to compute latencies of rSO2 change relative to seizure onset and termination. We investigated (1) whether there is a change in rSO2 prior to EEG and behavioral onset of the seizure, (2) the timing of onset of significant changes in rSO2 (in either direction) relative to EEG seizure onset and termination, (3) the magnitude of change of rSO2 in the periictal period and (4) the timing of rSO2 change relative to changes in SaO2 and ETCO2. As an additional control, to assess the interictal stability of the rSO2 signal, we compared 10 min of rSO2 data acquired shortly after application of the optodes (between 0900 and 1700) with 50 min of rSO2 acquire between midnight and 0050 and ensured that no seizure had occurred within 3 h of that recording.

Statistical analysis was performed using Sigmastat version 11 (Systat Software Inc.). A paired *t*-test was used to assess rSO2 change from baseline when data passed the Shapiro–Wilk test for normality. The nonparametric Wilcoxon Signed Rank test was used when data did not pass the normality test. *P* Values <0.05 were considered significant. Summary descriptive statistics are presented as mean ± standard deviation (median; range).

3. Results

VET recordings including usable synchronized rSO2 data were obtained in six patients for a total of eleven seizures. The mean seizure duration was 87 ± 46.4 s (66, 31–164). Six seizures were of left temporal onset, 5 of right temporal onset. Three left temporal onset seizures (in 3 patients) and two right temporal seizure proceeded to secondary generalization. All seizure onsets were ipsilateral to the NIRS sensor except for two. Relevant clinical data for the six patients are presented in Table 1.

For statistical analysis data from a single representative seizure for each patient was used except for one patient who had a left temporal partial seizure followed approximately 167 min later by a right temporal seizure with secondary generalization. For this patient data from both seizures were included in the analysis. Thus