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SHORT COMMUNICATION

Increased cerebral oxygenation precedes generalized tonic clonic seizures

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Summary Based on previous fMRI and SPECT studies, it has been suggested seizures may be preceded by increased cerebral blood flow. Recently, we demonstrated transcutaneous regional cerebral oxygen saturation (rSO2) sensors are feasible for use in patients undergoing video EEG monitoring. We reanalyzed our data to determine if seizures were consistently marked by increased cerebral oxygenation. Patients with histories of generalized tonic clonic seizures (GTCS) were recruited into our study. All subjects were evaluated with continuous 30-channel scalp EEG and 2 rSO2 sensors placed on each side of the forehead. We calculated the mean rSO2 value for the 1 h epochs in the non-ictal (2 h prior to seizure onset) and pre-ictal (1 h prior to onset) periods. Seven primary/secondarily GTCS from 5 patients were captured. The mean rSO2 value in the non-ictal period was $75.6 \pm 5.7\%$. This increased to $76.0 \pm 6\%$ in the pre-ictal period ($p = 0.032$). Four of the 7 GTCS (57.1%) were marked by $\geq$3 sequential rSO2 values in the pre-ictal period that were $\geq$3 SDs greater than the mean non-ictal rSO2 value. Three GTCS (42.9%) were marked by sustained cerebral hyperemia for $\geq$15 consecutive readings. Our results suggest increased cerebral blood flow could be non-invasively used to predict seizure occurrence.

Introduction

One of the most devastating aspects of uncontrolled seizures is their lack of predictability. Without warning, patients can be rendered unable to respond to the outside world. When seizures involve impairment of motor ability and/or awareness, it may limit a patient's ability to function independently. This may include the ability to drive and/or perform essential tasks related to employment. Unpredictable seizures can also put patients at increased risk for morbidity and mortality. This includes seizure-related falls,

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motor vehicle accidents, drowning, and sudden unexpected death in epilepsy (SUDEP). If patients had a reliable way to determine when a seizure was likely to happen, they could potentially take steps to prevent such seizures. This could include the preemptive administration of benzodiazepines and/or increased doses of their existing antiepileptic drugs (AEDs). Accurate seizure prediction could also allow the patient and family/caregivers the opportunity to minimize injury should the seizure still occur.

Currently, there is no non-invasive tool that reliably predicts the occurrence of seizures. When designing such tools, it may be useful to examine cerebral blood flow (CBF). During invasive studies with cortical surface CBF and electrocorticographic monitoring, increases in CBF have been shown to precede the clinical onset of temporal lobe seizures (Weinand et al., 1994). Such CBF increases have been confirmed in imaging studies of patients with seizures utilizing single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) (Baumgartner et al., 1998; Federico et al., 2005). These changes have generally been documented several minutes prior to clinical/electrographic seizure onset, a time period that would potentially permit the implementation of abortive and/or protective strategies.

Accordingly, we reanalyzed data from a previous study of non-invasive cerebral tissue oximetry in our Epilepsy Monitoring Unit. We sought to determine if convulsive seizures were consistently marked by increased cerebral oxygenation. If true, such technology could theoretically one day be used to non-invasively predict seizure occurrence.

Methods

We performed a reanalysis of data gathered during a feasibility study of non-invasive cerebral tissue oximetry in patients with primary or secondarily generalized tonic clonic seizures (GTCS) (Moseley et al., 2012). Subjects were evaluated with continuous 30-channel scalp EEG and two transcutaneous regional cerebral oxygen saturation (rSO2) sensors placed on each side of the forehead. Data from the rSO2 sensors were recorded every 4 s by a Nonin Equanox Model 7600 Regional Oximeter (Nonin, Plymouth, MN, USA). We calculated the mean rSO2 value from the most reliable sensor for the 1 h epochs in the non-ictal (2 h prior to seizure onset) and pre-ictal (1 h prior to seizure onset) periods. We determined the occurrence and timing of rSO2 values in the pre-ictal period that were $\geq$3 standard deviations (SDs) from the mean rSO2 value calculated in the non-ictal period.

All data entry and statistical analysis were performed using IBM SPSS Statistics Version 19 (IBM, Armonk, NY, USA). We utilized the independent-samples Student's *t*-test (2 tailed) for continuous data. *P*-values <0.05 were considered statistically significant.

This study was approved by the Institutional Review Board of Mayo Clinic, Rochester. Written informed consent was obtained from all subjects.

Results

Five patients underwent prolonged video-EEG and rSO2 monitoring, during which 7 primary or secondarily GTCS with usable data were captured. The mean rSO2 value in the non-ictal period was 75.6 $\pm$ 5.7%. This significantly increased to 76.0 $\pm$ 6% in the pre-ictal period ($p = 0.032$). Four of the 7 GTCs (57.1%) were marked by at least 3 sequential rSO2 values in the pre-ictal period that were $\geq$3 SDs greater than the mean rSO2 value recorded during the non-ictal period (see Fig. 1). On average, such values were noted 18 min 30 s (18:30) prior to electrographic seizure onset (range 7:40—33:54). The maximum pre-ictal rSO2 values for these 4 seizures (mean 83.5%, range 76—90%) were recorded a mean of 18:17 prior to seizure onset (range 6:00—33:38). Three GTCS (42.9%) were marked by sustained hyperoxia for 8 or more consecutive readings. Such sustained readings were noted a mean of 16:13 prior to seizure onset (range 7:20—33:34). All 3 of these GTCS were also marked by sustained cerebral hyperoxia for $\geq$15 consecutive readings. Such sustained readings were noted a mean of 15:45 prior to seizure onset (range 6:52—33:06). All recorded elevations in cerebral oxygenation resolved prior to seizure onset.

Discussion

Based on our data, increased cerebral oxygenation as measured by non-invasive rSO2 sensors frequently precedes convulsive seizures. The majority of recorded GTCS were marked by multiple sequential pre-ictal rSO2 values in the top 0.1% of the non-ictal values. Such values were sustained, with all but one of those GTCS being marked by continuous cerebral hyperoxia for at least 60 s. Similar findings were observed during a previous study of non-invasive cerebral tissue oximetry (Seyal, 2014). In that study, temporal lobe seizures from 6 patients were marked by a mean pre-ictal rSO2 increase of 7.1%. Similar to our cohort, such changes occurred several minutes (mean 4.98 min) prior to seizure onset (Seyal, 2014). Such findings correlate well with imaging and intracranial studies, some of which have documented increased CBF up to 20 min prior to ictal onset (Weinand et al., 1994; Baumgartner et al., 1998; Federico et al., 2005).

Our results suggest the potential value of non-invasive cerebral tissue oximetry in predicting seizure occurrence. Although the technology of transcutaneous rSO2 monitoring was originally validated in patients undergoing carotid endarterectomy, it has shown increasing promise in additional clinical settings. These include the monitoring and prognostication of patients in the neurologic intensive care unit and status post cardiac arrest (Bhatia and Gupta, 2007; Parnia et al., 2012). If confirmed in larger studies, our findings suggest such technology could one day be used to alert patients of an increased risk of impending seizures. This is particularly relevant given the prolonged period of time (over 18 min prior to seizure onset in our cohort) over which significantly increased CBF occurred. Such an alert could allow patients and/or caregivers to administer additional antiseizure drugs or rescue medications to potentially prevent seizures. In the past, usage of rescue benzodiazepines within such a time window might have been limited to the intravenous route (given the more prolonged time to peak action of oral and intramuscular formulations). However, with the advent of nasal formulations (such as intranasal