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SHORT COMMUNICATION

Increased cerebral oxygenation precedes generalized tonic clonic seizures

Brian D. Moseley[a,*], Jeffrey W. Britton[b,1], Elson So[b,1]

[a] Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH, USA
[b] Division of Epilepsy, Department of Neurology, Mayo Clinic, Rochester, MN, USA

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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 ± 5.7%. This increased to 76.0 ± 6% in the pre-ictal period (p = 0.032). Four of the 7 GTCS (57.1%) were marked by ≥3 sequential rSO2 values in the pre-ictal period that were ≥3 SDs greater than the mean non-ictal rSO2 value. Three GTCS (42.9%) were marked by sustained cerebral hyperemia for ≥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,

* Corresponding author at: 260 Stetson Street, Suite 2300, Cincinnati, OH 45267-0525, USA. Tel.: +1 513 558 5440; fax: +1 513 558 4305.
E-mail addresses: briandmoseley@gmail.com (B.D. Moseley), britton.jeffrey@mayo.edu (J.W. Britton), eso@mayo.edu (E. So).
[1] 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 774 4458; fax: +1 507 266 4752.

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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

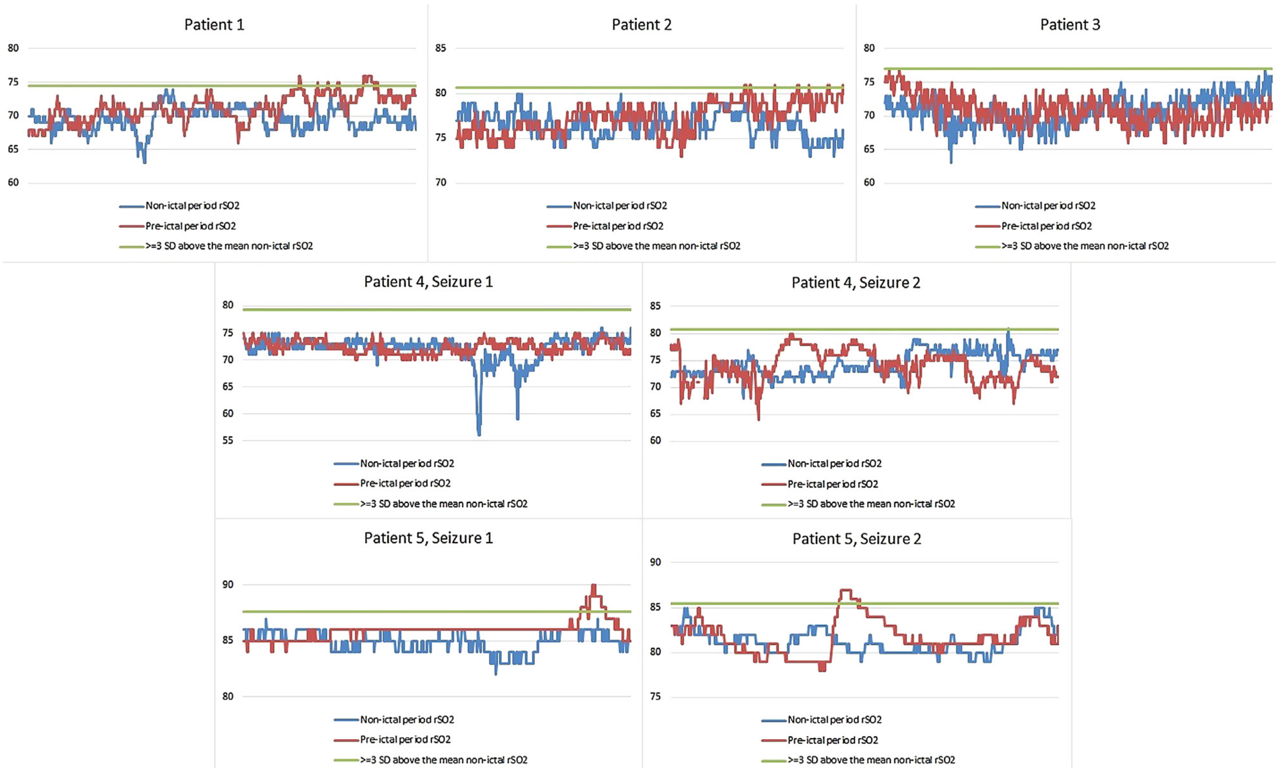

Figure 1 Regional cerebral oxygen saturation values in non-ictal versus pre-ictal periods. *Key*: rSO2 = regional cerebral oxygen saturation. rSO2 values are plotted on the vertical axis. Time is displayed on the horizontal axis. The data point furthest to the left indicates either 2 h prior to seizure onset for the non-ictal period or 1 h prior to seizure onset for the pre-ictal period.

midazolam, which has a mean time to peak action of 14 min), such a warning time could now be clinically useful (Knoester et al., 2002).

Even if unsuccessful, such a warning could allow patients and caregivers to minimize hazards in their surroundings that increase the risk of injury. For example, a prolonged warning could allow otherwise unimpaired patients who are operating a motor vehicle to pull to the side of the road, disable their vehicles, and call for help. If such predictions were reliable, it could redefine driving restrictions and reporting requirements for those with uncontrolled seizures. In addition, seizure prediction devices based on non-invasive cerebral tissue oximetry recordings could replace detection devices as the preferred way for families and caregivers to monitor for seizure activity. If more accurate, rSO2 recording devices could allow family members and caregivers to preemptively position patients in ways to minimize the development of seizure-related injuries. This could be especially pertinent for nocturnal seizures, where something as simple as supervision and stimulation (e.g. rolling the patient on his/her side) may reduce the risk of SUDEP (Langan et al., 2005).

In addition to insights about seizure prediction, our results may shed more light on the pathophysiology of seizure initiation. Our findings suggest that seizures may require factors promoted by cerebral hyperemia to occur. These include increased neuronal glucose, improved mitochondrial metabolism, and increased ATP production. All of these may increase neuronal excitability via activation of sodium/potassium ATPases, closing of potassium channels, increased glutamate receptor activation, and removal of endogenous inhibitory mediators such as adenosine and endocannabinoids (Lado and Moshe, 2008). In addition, the removal of excess hydrogen ions by increased cerebral perfusion may contribute to seizure initiation. It is thought that acidosis may contribute to seizure prevention/termination via impairment of NMDA receptor function, activation of acid-sensitive TASK-type potassium channels, uncoupling of connexins, and diminishment of gap junction conductance (Lado and Moshe, 2008). If confirmed in larger studies, such findings may assist with the future development of novel AEDs.

Our study was not without limitations. Given that the data was obtained from a feasibility study with a small sample size, robust statistical analyses could not be performed. Larger studies will be needed to assess whether or not increased cerebral oxygenation, as measured with non-invasive rSO2 sensors, can reliably predict the occurrence of convulsive seizures. In addition, our study limited its analysis to GTCS. Therefore, we cannot make conclusions about whether other types of seizures (e.g. focal dyscognitive seizures) are marked by pre-ictal increases in CBF. Such seizure types can be just as physically and socially disabling as GTCS and worthy of accurate prediction. However, despite these limitations, the findings of our study deserve notice. Given the potential medical and psychosocial benefits, further exploration of cerebral hyperemia in seizure prediction is needed.

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References

Baumgartner, C., Serles, W., Leutmezer, F., Pataraia, E., Aull, S., Czech, T., Pietrzyk, U., Relic, A., Podreka, I., 1998. Preictal SPECT in temporal lobe epilepsy: regional cerebral blood flow is increased prior to electroencephalography-seizure onset. J. Nucl. Med. 39, 978—982.

Bhatia, A., Gupta, A.K., 2007. Neuromonitoring in the intensive care unit: II. Cerebral oxygenation monitoring and microdialysis. Intensive Care Med. 33, 1322—1328.

Federico, P., Abbott, D.F., Briellmann, R.S., Harvey, A.S., Jackson, G.D., 2005. Functional MRI of the pre-ictal state. Brain 128, 1811—1817.

Knoester, P.D., Jonker, D.M., Van Der Hoeven, R.T., Vermeij, T.A., Edelbroek, P.M., Brekelmans, G.J., de Haan, G.J., 2002. Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. Br. J. Clin. Pharmacol. 53, 501—507.

Lado, F.A., Moshe, S.L., 2008. How do seizures stop? Epilepsia 49, 1651—1664.

Langan, Y., Nashef, L., Sander, J.W., 2005. Case-control study of SUDEP. Neurology 64, 1131—1133.

Moseley, B.D., Britton, J.W., Nelson, C., Lee, R.W., So, E., 2012. Periictal cerebral tissue hypoxemia: a potential marker of SUDEP risk. Epilepsia 53, e208—e211.

Parnia, S., Nasir, A., Shah, C., Patel, R., Mani, A., Richman, P., 2012. A feasibility study evaluating the role of cerebral oximetry in predicting return of spontaneous circulation in cardiac arrest. Resuscitation 83, 982—985.

Seyal, M., 2014. Frontal hemodynamic changes precede EEG onset of temporal lobe seizures. Clin. Neurophysiol. 125, 442—448.

Weinand, M.E., Carter, L.P., Patton, D.D., Oommen, K.J., Labiner, D.M., Talwar, D., 1994. Long-term surface cortical cerebral blood flow monitoring in temporal lobe epilepsy. Neurosurgery 35, 657—664.