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ORIGINAL ARTICLE

Limitations of Threshold-Based Brain Oxygen Monitoring for Seizure Detection

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Abstract
Background Brain tissue oxygen ($PbtO_2$) monitors are utilized in a threshold-based fashion, triggering actions based on the presumption of tissue compromise when $PbtO_2$ is less than 20 mmHg. Some early published practice guidelines suggest that seizure is a potential culprit when $PbtO_2$ crosses this threshold; evidence for this is not well defined.
Methods Data were collected manually as part of a prospective observational database. $PbtO_2$ monitors and continuous electroencephalogram (cEEG) were placed by clinical protocol in aneurysmal subarachnoid hemorrhage (aSAH) or traumatic brain injury (TBI) patients with a Glasgow Coma Scale (GCS) ≤ 8. Eight patients with discrete seizures during an overlapping monitored period were identified. Probability of seizure when $PbtO_2$ value was <20 mmHg (and the inverse) were calculated.
Results There were 343 distinct seizure episodes and 1797 $PbtO_2$ measurements. 8.9% of seizures were followed by a $PbtO_2$ value below 20 mmHg. Of all observed low $PbtO_2$ values, 3.8% were associated with seizure. Seizure length did not influence $PbtO_2$. Two patients with the highest number of seizures developed low $PbtO_2$ values post-seizure.
Conclusions Seizures were neither associated with a $PbtO_2$ value of <20 mmHg nor associated with a drop in $PbtO_2$ value across a clinically significant threshold. However, we cannot rule out the existence of *any* relationship between $PbtO_2$ and seizure with this limited data set. Prospective research using electronically recorded data is required to more effectively examine the relationship between $PbtO_2$ and seizure.

Keywords Traumatic brain injury · Physiologic monitoring · Subarachnoid hemorrhage · Non-convulsive seizure disorder · Oxygen/Metabolism · Brain injuries/physiopathology

Introduction

Non-convulsive seizures in the Neuro-Intensive Care Unit (neuroICU) are frequent, potentially harmful when prolonged [1–3], and lack a semiology to alert intensivists to their presence. Non-convulsive seizures are detected by scalp-EEG in up to 35% of neuroICU patients [4]. Recent evidence from depth electrodes suggests that the prevalence of non-convulsive seizures may be even higher [5]. A temporal relationship between non-convulsive seizures and other markers of secondary brain injury suggest a causal relationship—e.g., increased cerebral glutamate and glycerol [6], higher lactate/pyruvate ratio [7], and increased intracranial pressure associated with worsening midline shift [8].

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The routine use of cEEG is resource-intensive, and is limited by the technical aspects of lead application and maintenance and availability of around the clock expert analysis. Empiric cEEG monitoring generates large amounts of data, and the lack of high fidelity identification algorithms for seizure means that communication of harmful events relies upon the workflow of the expert EEG analyst who reviews the data sporadically. The potential for time delay in seizure detection is large. To justify the use of EEG to detect or confirm non-convulsive seizures, most intensivists currently rely upon their high suspicion, exclusion of other diagnoses, and suggestive changes in physiologic data. A real-time biometric for seizure would be a valuable asset to neurocritical care.

Brain tissue oxygen ($PbtO_2$) monitors are increasingly used to help manage severe brain injury [9]. While the device does provide continuous measurements, it is mostly used as a threshold-based alarm to prompt diagnostic interventions, based on the presumption of tissue compromise when $PbtO_2$ is less than 15 mmHg [10]. To avert tissue injury, most local protocols set a clinical threshold for therapeutic intervention at 20 mmHg.

It is known that seizures cause an increase in cerebral metabolic rate of oxygen ($CMRO_2$) [11, 12]. Anecdotal reports suggest that this can be reflected in a reduction of jugular venous oxygen saturation [13, 14]. Some published practice guidelines for $PbtO_2$ monitors suggest that a seizure is an important diagnostic consideration when $PbtO_2$ crosses below the threshold of 20–25 mmHg [15–18]. In the presence of intact flow-metabolism coupling, seizures induce a measureable increase of cerebral blood flow (CBF) that adequately matches the increased demand [12, 19–23]. While not an ischemia monitor or a monitor of CBF, $PbtO_2$ in part depends on CBF. In this study, we examined the relationship between $PbtO_2$ and seizure, hypothesizing that crossing a threshold was an overly simplistic model for the behavior of $PbtO_2$ in the context of seizure after brain injury.

Methods

Patient Population

Subjects included in this study were identified from a prospective observational database (Brain Oxygen Monitoring Outcome study) that describes patients with severe acute brain injury (GCS $\leq$ 8) treated in the neuroICU at an academic tertiary care Level 1 Trauma Center. Patients included in this study had: (1) non-penetrating TBI or aSAH; (2) both $PbtO_2$ and intracranial pressure (ICP) monitoring for $>$24 h; (3) overlapping cEEG and $PbtO_2$ monitoring; and (4) one or more discrete seizures during the monitored period. These patients were cared for between October 1, 2006, and February 28, 2009. Approval for the study was obtained from the Institutional Review Board.

Intracranial Monitors

ICP, brain temperature, and $PbtO_2$ were monitored continuously using commercially available devices (Integra Neuroscience, Plainsboro, NJ) as part of standard care when GCS was $\leq$8. Monitors were inserted through a burr hole into white matter that appeared normal on head CT and held in place with a triple-lumen bolt. In patients with aSAH, the monitors were placed on the side of expected maximal vasospasm based on aneurysm location and the distribution of subarachnoid blood. In patients with TBI, the monitors were placed on the side of maximum pathology. When there was no asymmetry in pathology on head CT, the monitors were placed in the right frontal region. If the patient had undergone a craniotomy, the probes were placed on the same side as the injury if the craniotomy flap allowed. Non-contrast head CT scans were performed within 24 h to confirm correct monitor placement (e.g. not in a contusion or infarct). Probe function and stability were confirmed by an appropriate $PbtO_2$ increase after an oxygen challenge (100% FiO_2). After an initial period of equilibrium, therapy was targeted to achieve an ICP of $<$20 mmHg and a $PbtO_2$ of $\geq$25 mmHg.

General Patient Care

Patients were managed in the neuroICU according to local protocols based on published recommendations for severe TBI, aSAH, and ICU care [24–26]. This included: (1) early identification and evacuation of space-occupying hematomas or placement of a ventriculostomy for hydrocephalus; (2) intubation and ventilation with FiO_2 and minute ventilation adjusted to maintain $SaO_2 > 93\%$ and to avoid $PaO_2 < 60$ mmHg when the GCS was $\leq$8; (3) $PaCO_2$ set at approximately 35–45 mmHg unless ICP was elevated when $PaCO_2$ was maintained between 30 and 40 mmHg; (4) sedation using propofol during the first 24 h, followed by sedation and analgesia using lorazepam, morphine, or fentanyl when ventilated; (5) normothermia ($\sim$35–37°C); (6) euvolemia using a baseline crystalloid infusion (0.9% normal saline, 20 mEq/l KCl); and (7) anticonvulsant therapy for 1 week or longer if clinical seizures were observed. Additional management for aSAH included: (1) early aneurysm occlusion using microsurgical or endovascular techniques; (2) daily TCDs; (3) administration of nimodipine for 21 days; and (4) further volume expansion using normal saline and albumin and induced hypertension for symptomatic vasospasm.

Management of $PbtO_2$

Patients received cause-specific therapy to correct compromised $PbtO_2$ (<20 mmHg). In general, steps were first taken to augment CBF. These included reducing elevated ICP through cerebrospinal fluid drainage, osmotic therapy (mannitol) and, when indicated, decompressive hemicraniectomy. The cerebral perfusion pressure (CPP) was increased with intravenous fluids and vasopressors. When regional CBF was compromised because of vasospasm refractory to standard medical measures after aSAH, patients were treated with intra-arterial nicardipine or papaverine, or with balloon angioplasty. When lung function was compromised, steps were taken to improve pulmonary gas exchange, e.g. increased FiO_2, optimization of other ventilator settings, and pulmonary toilette. When O_2 delivery was suboptimal due to anemia, packed red blood cells were administered.

Continuous EEG

Continuous 16-channel scalp-EEG was initiated by clinical protocol in aSAH patients with a Fisher grade 3 and/or GCS $\leq$ 8 between day 2 and 10, to detect ischemia. cEEG was additionally started in patients with documented vasospasm, increasing transcranial Doppler velocities, or in patients who required heavy sedation. In TBI patients, cEEG was initiated by clinical protocol in patients with a GCS $<$ 12 and intracranial hemorrhage, to detect subclinical seizures. Monitoring was discontinued if no seizures were detected in 48 h but could be continued for additional 48 h periods as pharmacological sedation was weaned.

Board-certified neurophysiologists experienced in ICU EEG-monitoring reviewed cEEGs at least twice daily. cEEGs were prospectively interpreted independent of $PbtO_2$ results. cEEG results were communicated to the primary team at least twice daily. cEEGs prospectively read as having discrete seizures were selected by querying our hospital's EEG lab database for all EEGs done during the study period. Entire cEEG tracing files were reviewed (RM, SS) for seizure onset and offset times and laterality. Electrographic seizures and status epilepticus were defined by existing criteria [27]. Paroxysmal epileptiform activity demonstrating frequency, morphology, and spatial evolution occurring in periods of >10 s supported classification of electrographic seizure. Frequency evolution >2–3 Hz also supported seizure classification. Status epilepticus was defined as seizure activity occurring $\geq$30 min. Patterns with SIRPIDs (stimulus-induced, rhythmic, periodic, or ictal discharges) were not counted as seizures.

Local Protocol for Nursing Documentation (ICP, CPP, and $PbtO_2$)

By clinical protocol, values of $PbtO_2$ were recorded at least every hour and every time an alarm indicated they were below a threshold of 20 mmHg, or coincident with another action that was being documented. For example, if a clinical event occurred or medication was being administered on the off-hour, all vitals (including $PbtO_2$) were recorded.

Data Collection and Statistical Analysis

To allow for intracranial probe equilibration, data from the first 6 h after $PbtO_2$ monitor insertion were discarded. Patients with status epilepticus were largely excluded because discrete onset and offset times were difficult to define. We used the Stata SE 10.0 statistical software program (Stata Corp) for data analysis. We calculated the probability of seizure given a $PbtO_2$ value less than 20 mmHg (and the inverse) for each patient.

Results

Patient Characteristics

Nineteen patients with seizures in the $PbtO_2$ database were screened for this study; eight patients whose seizures occurred during an overlapping monitored period (coincident $PbtO_2$ and cEEG) were included. Characteristics of these patients are described in Table 1. The median patient age was 62.5 years. Half of the patients were female. Five patients had aSAH and three had severe TBI. Median GCS on admission was 10. Six of the eight patients had $PbtO_2$ monitors ipsilateral to seizure focus.

Recorded Measurements

There were 343 distinct seizure episodes and 1,797 $PbtO_2$ measurements. Details of recorded measurements are listed in Table 2. There were a median of 29 seizure episodes per patient (interquartile range (IQR): 10.75, 69.75), each lasting for a median of 110 s (IQR: 45 s, 292 s). There were a median of 231 $PbtO_2$ measurements recorded per patient (IQR: 133, 276.25). Of these $PbtO_2$ measurements, only 23 (median per patient) were <20 mmHg (IQR: 24 for aSAH; 22 for TBI).

The intracranial physiological variables recorded during the patients' course are listed in Table 3.

Table 1 Patient characteristics

Patient #	Age (years) gender	Dx	Admission GCS	Fisher Grade	ICH or Contusion	Side of $PbtO_2$ monitor	Number of $PbtO_2$ measurements	Side of seizure Focus	Number of Seizures	Surgery	Aneurysm occluded	Symptomatic vasospasm	Mortality at 30 days
1	72 M	aSAH	15	3	No	R	388	L	60	No	ACOM (coil)	Yes	Yes
2	70 M	aSAH	7	3	No	R	148	B	7	No	No	No	Yes
3	47 F	aSAH	13	4	L	R	235	B	6	L-clot evacuation & clip	L MCA	Yes	No
4	75 F	aSAH	10	4	L	R	80	R	101	L-clot evacuation & clip	L PCOM & L MCA	No	No
5	55 F	aSAH	14	2	No	R	392	B	12	R-Clip	R MCA	Yes	No
6	20 M	TBI	3	–	No	R	227	R	15	No	–	–	No
7	55 F	TBI	3	–	No	L	239	R	43	R-subdural evacuation	–	–	No
8	73 M	TBI	10	–	B	R	88	R	99	R-DHC, anterior temporal lobectomy	–	–	Yes

R right, *L* left, *B* bilateral, *ICH* intracerebral hematoma, *DHC* decompressive hemicraniectomy *PCOM* posterior communicating artery, *ACOM* anterior communicating artery, *MCA* middle cerebral artery

Compromised $PbtO_2$ After Seizure: Sampling Various Time Windows

We examined the probability that a seizure resulted in a $PbtO_2$ value below 20 mmHg. Examining every seizure as an independent event, we identified all $PbtO_2$ readings within an hour, half hour, or 15 min windows after seizure onset. Only 9.8% of seizures were followed by a $PbtO_2$ value below 20 mmHg within an hour (30 of 305 seizures with any $PbtO_2$ value recorded within an hour). 9.6% were followed by a $PbtO_2$ value below 20 mmHg within 30 min (19 of 196 seizures with any $PbtO_2$ value recorded within 30 min). 8.9% were followed by a $PbtO_2$ value below 20 mmHg within 15 min (10 of 112 seizures with any $PbtO_2$ value recorded within 15 min).

Change in $PbtO_2$ After Seizure

We calculated the magnitude of $PbtO_2$ change from seizure onset to 15 min after seizure onset. The mean change in $PbtO_2$ was a decrease of 0.63 mmHg, or nearly zero (Fig. 1). If seizure was always associated with a drop in $PbtO_2$, we would expect the data to be skewed to the left; instead, an approximately normal distribution can be observed for those cases where a change in $PbtO_2$ value did occur, with the peak around 0. A chi-square test indicates that the values are likely drawn from a normal distribution (chi-square = 1.0).

Crossing the Threshold

$PbtO_2$ is typically used in a threshold-based way in the neuro-ICU (therapy is initiated when $PbtO_2$ is <20 mmHg). Therefore, we examined the probability that the $PbtO_2$ value dropped from above to below the threshold after the seizure. When only seizures whose minimum $PbtO_2$ value in the preceding hour was >20 mmHg were examined, only 6.4% (17 seizures out of 262) were associated with a $PbtO_2$ value <20 mmHg in the hour after. These data suggest that very few seizures would presumably trigger an alarm in clinical practice.

Influence of Seizure Duration

We grouped seizures by duration to examine if longer seizures were associated with a greater $PbtO_2$ change than shorter seizures (Table 4). The mean change of $PbtO_2$ was $+0.45$, -0.16, and -0.65 mm Hg for seizures <1 min, between 1 and 5 min, and >5 min, respectively.

Cumulative Effect of Seizures Within Patients; Non-Independence

Noting that the $PbtO_2$ values may reflect the cumulative effect of multiple seizures (i.e. non-independence), we

Table 2 Recorded measurements

	aSAH	TBI	All (medians, IQR)
Seizure episodes (number per patient)	12 (IQR: 7, 60)	43 (IQR: 29, 71)	29 (IQR: 10.75, 69.75)
Seizure length (seconds)	180 s (IQR: 50, 540)	65 s (IQR: 40, 176)	110 s (IQR: 45, 292)
$PbtO_2$ measurements (number per patient)	235 (IQR: 148, 388)	227 (IQR: 157.5, 233)	231 (IQR: 133, 276.25)
$PbtO_2 < 20$ mmHg (number per patient)	24 (IQR: 21, 75)	22 (IQR: 16.5, 32.5)	23 (IQR: 20, 51)

Table 3 Intracranial physiological variables

Clinical variable	aSAH ($n = 5$)	TBI ($n = 3$)	All
ICP (mmHg)			
Mean ± SD	9.97 ± 8.06	11.02 ± 7.16	10.39 ± 7.73
Min	0	0	0
Max	66	59	66
$PbtO_2$ (mmHg)			
Mean ± SD	25.21 ± 6.90	30.96 ± 15.84	27.33 ± 11.41
Min	3	3	3
Max	69.1	161	161

Table 4 $PbtO_2$ change after seizure, categorized by seizure duration

	Seizure <1 min	Seizure >1, <5 min	Seizure >5 min
Mean change (mmHg) ± SD	0.45 ± 3.78	−0.16 ± 4.5	−0.65 ± 5.16

clustered values by patient. We found that all the episodes of post-seizure $PbtO_2 < 20$ mmHg except for one, occurred in Patient #8 who had 99 discrete seizures. The decrease in $PbtO_2$ occurred late in the flurry of seizures (Fig. 2).

This might imply that low $PbtO_2$ can still be a late marker of prolonged or numerous seizures, and thus might be useful as a threshold-based monitor. However, examination of the other patient (patient #4) with post-seizure $PbtO_2 < 20$ mmHg did not support this. In this patient, 101 discrete seizures were observed, and yet there was only a single post-seizure $PbtO_2$ value <20 mmHg, and no clear trend toward brain hypoxia was observed (Fig. 3).

Sidedness of Monitor to Seizure Location

In our ICU, we attempted to place $PbtO_2$ monitors, when possible, ipsilateral to the side of maximal pathology in TBI. Seizures are likely to start in the area of focal injury but may then spread to the other hemisphere. In aSAH patients, unless there was focal injury, the monitor always was placed in the right frontal region. Six of the eight patients had $PbtO_2$ monitors ipsilateral to areas involved in seizure (either focal seizures or generalized). Two patients had contralateral monitors. One patient (patient #1) had aSAH and 65 seizures; none occurred within an hour of

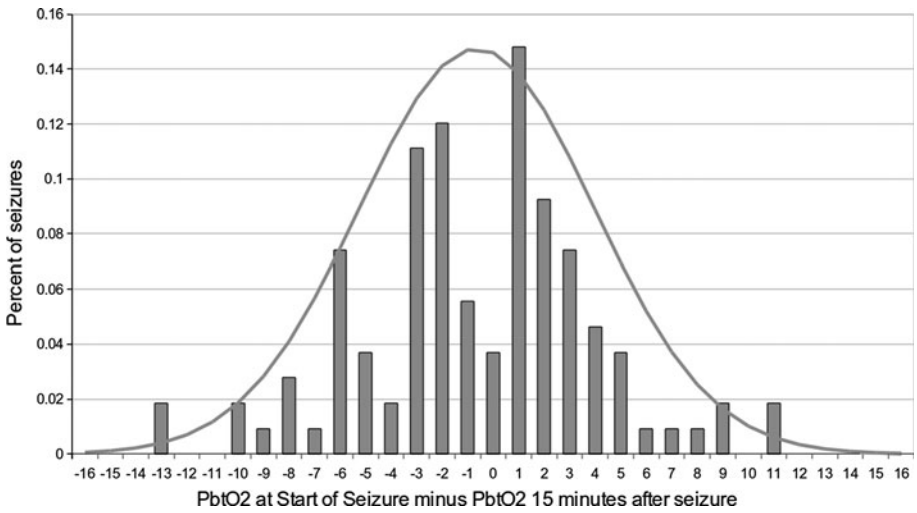

Fig. 1 Change of $PbtO_2$ with seizure. Histogram illustrating change of $PbtO_2$ with cEEG identified seizure. The frequency of occurrence of each magnitude of change (rounded up to nearest integer). A normal curve with the same mean as the data is superimposed for reference

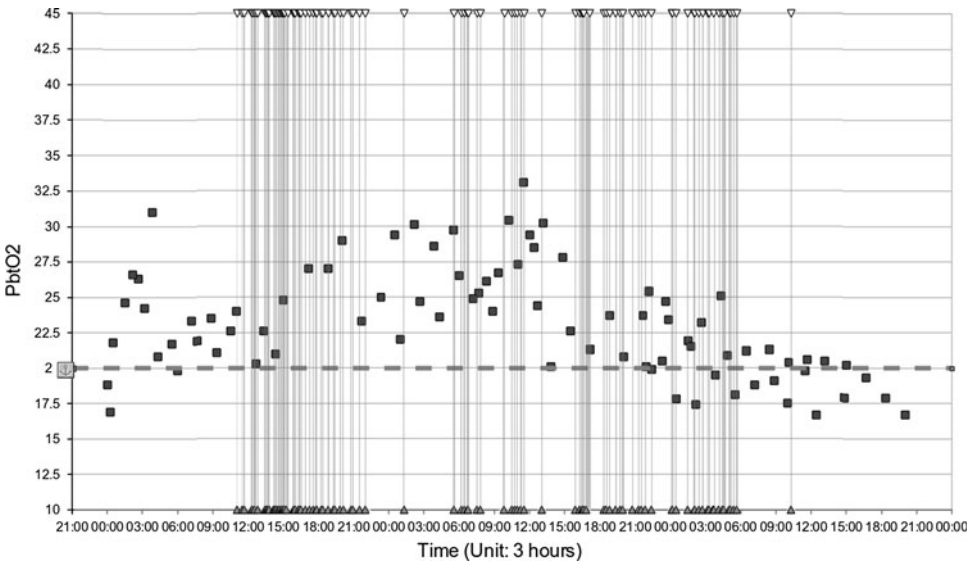

Fig. 2 $PbtO_2$ values graphed over time in Patient #8, with 99 discrete seizures and virtually all noted episodes of post-seizure $PbtO_2 < 20$ mmHg in our data set. The *x*-axis represents time in 3 h increments, and the *y* axis is $PbtO_2$ values. The $PbtO_2$ clinical threshold of 20 mmHg is indicated with a horizontal *dashed line*. Seizure onsets and offsets are labeled with *triangles*, *vertical bars* represent duration of seizures. $PbtO_2$ measurements are *squares*

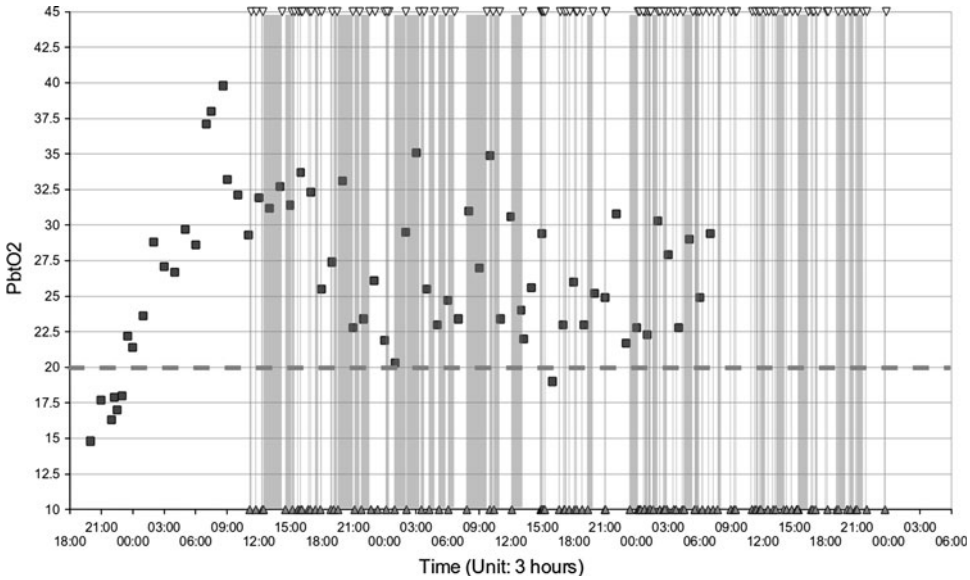

Fig. 3 $PbtO_2$ values graphed over time in Patient #4 with 101 discrete seizures. The *x*-axis represents time in 3 h increments, and the *y*-axis is $PbtO_2$ values. The $PbtO_2$ clinical threshold of 20 mmHg is indicated with a *horizontal dashed line*. Seizure onsets and offsets are labeled with *triangles*, *vertical bars* represent duration of seizures. $PbtO_2$ measurements are *squares*

compromised $PbtO_2$. The second patient (patient #7) had TBI and 44 seizures; none occurred within an hour of compromised $PbtO_2$.

Conclusion

Seizures, including non-convulsive seizures, may lead to further secondary brain injury. The ability to detect these events utilizing existing monitors would be of potential benefit to the practice of neurocritical care. Previous clinical guidelines have suggested that a $PbtO_2$ value <20 mmHg should elicit a differential that includes a seizure. In this study of 8 patients with discrete seizures, we did not observe a relationship between seizure activity on cEEG and threshold $PbtO_2$ values recorded in routine clinical practice.

The assumption that seizure is a possible cause of compromised $PbtO_2$ is not without consequence since it may lead to inappropriate resource utilization (cEEG monitoring) and antiepileptic administration. Additionally, it may give a sense of false reassurance regarding the absence of non-convulsive seizures in the setting of normal $PbtO_2$.

The expectation that $PbtO_2$ would simply decrease in response to seizure ignores the phenomenon of metabolic coupling—that reactive cerebral blood flow will deliver more oxygen to compensate for increased metabolic utilization. This is likely further dependent on the degree of brain injury and its effect on state of coupling. The as yet incompletely understood spatiotemporal hemodynamic response in human seizures, especially in acute brain injury, makes the attribution of brain hypoxia to seizure unresolved.

The precise impact of prolonged non-convulsive seizures on patient outcome is not well established [28]. However, some animal histopathological and human radiographic studies support the potentially harmful nature of prolonged non-convulsive seizure activity [1, 2]. It has also been suggested that increased seizure duration may be associated with worse outcome [29]. This has justified early treatment. While our data do not support a simplistic threshold-based relationship between $PbtO_2$ and seizure onset, it does suggest that a cumulative burden of seizures could be correlated with low $PbtO_2$. Whether this is an epiphenomenon or a primary process causing both is impossible to determine with this type of data.

Limitations

Our study has several potential limitations. First, $PbtO_2$ and vital sign measurements recorded by nursing staff several times an hour may be suboptimal to reflect changes caused by seizures lasting only 110 s (median length). By clinical protocol, nursing staff were directed to record every time an alarm indicated $PbtO_2$ values below a threshold of 20 mmHg. Our assumption was that every threshold crossing was documented. It is impossible to retrospectively quantify the duration or intensity of abnormal values that would trigger nursing documentation. It is likely proportional to the nurses' gestalt suspicion that the abnormal value holds clinical significance. In this way, documentation is likely biased. If short seizures caused transient decreases in $PbtO_2$, these drops may either have gone unnoticed or not concerned the nurses enough to warrant recording.

Second, we only included patients we identified as having seizures, rather than examining $PbtO_2$ values of patients unaffected by seizures. However, adding patients to the analysis who did not have seizures would only reduce the percentage of $PbtO_2$ values <20 mmHg which were preceded by a seizure. Since we were unable to find a correlation in this highly selected population, it seems unlikely that crossing a threshold $PbtO_2$ value of 20 is a sensitive indicator for seizure in a broader population. It remains unclear if patients with lower median $PbtO_2$ values are more likely to have acute seizures compared to patients without seizures.

Third, patients included in this analysis were identified retrospectively, thus we were limited to cEEG data that were collected according to the general protocol in the hospital. Fourth, it is possible that the differences in brain injury mechanisms and lesions between the two disease groups and the limited number of patients in each group may not allow for sufficient power to determine the change in $PbtO_2$ with seizures. We tried to compensate for this by performing the analysis on a large set of seizures from multiple patients. This study's results should allow for better powering in future studies. Unfortunately, the relative rarity of patients who fit our criteria (concomitant $PbtO_2$ and cEEG monitoring) made a larger sample size unobtainable. Fifth, it is possible that brief or deep seizures not detectable on scalp-EEG but by intracranial surface or depth electrode recording may allow for a better association between seizure and $PbtO_2$. Sixth, this was not a pure observational study in that patients received active treatment for compromised $PbtO_2$. Whether this influences our results is unclear.

Implications of Our Findings

The present work suggests that $PbtO_2$ interpretation based on simple threshold analysis has limited use for seizure detection. Nor can it provide assurance for absence of seizure. Higher sampling rates of $PbtO_2$ data may reveal finer correlations with seizure onset and offset. We posit that the response of brain oxygen in the context of seizure is more complicated than the crossing of a fixed threshold (specifically, a $PbtO_2$ of 20 mmHg). Future work that includes non-linear analysis of electronically recorded continuous $PbtO_2$ data is necessary to determine if this parameter may serve as an alternative indicator for seizure. Further study will be needed to determine whether patients with severe TBI or aSAH and a longer cumulative burden of seizure are at greater risk for brain hypoxia.

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