

Threshold-based Use of Brain Oxygen Monitor and Seizure Detection

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Abstract

Brain tissue oxygen (PbtO₂) monitors are threshold-based, and so trigger actions based on presumption of tissue compromise when PbtO₂ is less than 20 mmHg. Some published practice guidelines suggest that a seizure is a potential culprit when PbtO₂ crosses this threshold. The evidence for this assumption is slim.

Data were collected as part of a prospective observational database. PbtO₂ monitors and continuous EEG were placed by clinical protocol in patients with aneurysmal subarachnoid hemorrhage (aSAH) or traumatic brain injury (TBI) and a Glasgow Coma Scale of less than 8. Eight of these patients had one or more discrete seizures during an overlapping monitored period (both PbtO₂ and EEG) and were selected for review. Probability of seizure given PbtO₂ value less than 20 mmHg (and the inverse) were calculated by logistic regression, clustered by patient.

There were 274 distinct seizure episodes and 1797 PbtO₂ measurements in 8 patients (5 aSAH, 3 TBI, mean age $x + y$ years). Two of 7 patients had oxygen monitors contralateral to seizure focus (both TBI). In 17 of 180 (9.4%) of seizures (17/180) PbtO₂ became less than 20 within subsequent the 30 minutes (CI=0-26%). Conversely, in 2.5% of the PbtO₂ > 20 measurements (8/315) a seizure was detected seizure in the 30 minutes preceding PbtO₂ > 20mmHg.

We found that compromised PbtO₂ in brain-injured patients was not correlated with seizure. The limitations of brain oxygen monitors to detect seizure may be in their threshold-based interpretation. We propose prospective research for more effective strategies of interpreting patient data.

1 Introduction

The brain can be considered roughly to follow a supply and demand model. That is, the oxygen supply to the brain minus the cerebral metabolic oxygen rate of oxygen consumption (CMRO₂) is the brain oxygen measure. The current assumption is that seizure leads to an increased demand for oxygen in the brain due to excess activity, and thus an increased CMRO₂. Thus, the PbtO₂ drops, and a drop might be indicative of

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the intense cerebral activity associated with seizure. This presumption, however, stems directly from data with Venous Oxygen Saturation (SjVO₂) and seizure incidence. It has not been shown directly. In fact, this ignores the fact that reactive cerebral blood flow (CBF) will deliver more oxygen to compensate in a patient whose CBF response is not impaired. [[REF]] The as yet incompletely understood spatiotemporal hemodynamic response in human seizures makes the attribution of a drop in PbtO₂ to seizure dubious. Furthermore, care is often established through the use of threshold based monitors which alarm when PbtO₂ drops below a fixed level of 20 mmHg. This paper calls into question the validity of utilizing an ischemic threshold as a model for the response of PbtO₂ in the context of seizure.

Convulsive seizures can occur in brain injured patients at a rate of up to 27% [[REF]]. If non-convulsive seizures are considered, that rate goes up to 37% [[REF]], and it is highly likely that the statistic is higher, given that some likely go undetected. The best evidence available correlates seizures (both convulsive and non-convulsive) with worse outcome. [[REF]]. This may be a marker of injury severity, but it is more likely that it is causal [[REF]].

The reason for attempts to diagnose seizure using PbtO₂ stem from the inadequacy of relying on electroencephalography (EEG). The technical aspects of applying EEG leads and resource-intensive nature of expert analysis of the large amounts of data produced has proved to be prohibitive for widespread use as a detection tool for subclinical events such as nonconvulsive seizure [[REF]]. The time delay in receiving the results of the EEG are simply too great for them to be relied on in emergency circumstances in a critical care environment. Thus, alternative indicators for seizure based on data available in real time are valuable assets to neurocritical care. PbtO₂ was seized upon as one of a number of such alternative indicators, as focal measurement of PbtO₂ is regularly utilized in management of severe brain injury.

In order to measure PbtO₂, a LICOX probe is often used. The LICOX system is an intercranial probe designed by Integra to measure interstitial PbtO₂. The probe is inserted approximately 35 mm below the dura into the white matter of the brain. As with any intercranial probe, LICOX is accompanied by risk of [[XYZ]] [[ASK SOOJIN: Infection? Other poor outcomes?]] Brain oxygen readings measured utilizing LICOX are focal by definition, but the assumption is that generalized seizure would have global effects of which the focal LICOX monitor would be representative. For example, the CBF increase is thought to be nonspecific and therefore deliver more blood, and thus oxygen, to the entire brain. [[(although BOLD signal MAY be focal, it would be contaminated initially by this nonspecific overshoot and CBV response, perhaps later images could be more focalizing) /what does this mean? -alex]].[[REF?]] [[Standards of Care, how they're established?]] [[ASK SOOJIN]]

LICOX is thus used to detect seizures. Utilizing a threshold based alarm upon brain oxygen drop below 20 as a possible indicator of seizure might lead to caretakers leaving the LICOX in a patient "in case" a seizure occurs, which unnecessarily increases the risk for complications due to the invasive nature of the probe.

Though the EEG provides a gold standard for seizure detection, it would be valuable to have a method of detecting seizure utilizing more conventional, readily available data streams. A wealth of such patient data streams are now being captured, including patient records, laboratory results, and continuous vital sign signals. Given the afford-

ability of computational power which enables large amounts of data to be processed efficiently, it is conceivable that a new standard of care could be established for detection of seizure, utilizing these data streams. Such a standard would be more accurate than the threshold based warning alarms currently in use, and would be available for use more quickly than the gold standard expert reading of EEG data. LICOX values could play an important role in such a system, if the system utilizes more than a simple threshold. Very few if any studies have explored aspects of the continuous data stream produced by LICOX which help identify clinically significant changes in phenotypic state.

2 Hypothesis

We propose that the response of brain oxygen in the context of seizure is more complicated than the crossing of a fixed threshold (specifically, a PbtO₂ of 20).

We propose that brain oxygen will not necessarily dip, and may in fact change unpredictably in response to seizure. Whereas globally, cerebral metabolic demand may go up, delivery of blood to those areas would increase, whereas sum total of consumption would be reflected in drop in SjVO₂. Consequently, we predict PbtO₂ to behave thusly: a slight dip from baseline initially, upon onset of seizure; seconds later, CBF compensates for the drop and produces a normalization, or an increase (overresponse) to the drop; based on the length of the seizure, the blood oxygen falls, reaching baseline. This ability to compensate for the drop would be based on the ability for CBF to compensate for decreased brain oxygen by increased CBF, which in turn is affected by the health of the underlying brain. Thus, we propose that a threshold-based alarm is not appropriate evidence for seizure.

[[This wasn't really our hypothesis.... since we didn't actually test for this! We just tested for the first part. What's the right way to phrase this?]]

[[A GRAPH MIGHT BE NICE TO HAVE HERE, OF THE PROPOSED SHAPE OF THE PbtO₂ CURVE. THEN WE COULD PUT, AS A CAPTION: A stimulus (increased metabolic demand of cortical electrical impulse) is followed quickly by response (in the form of increased CBV delivery), which is represented in a trending data graph as an initial (transient) dip followed by an overshoot and an undershoot.]]

This hypothesis is supported by several studies. [[fMRI data shows overshoot, then undershoot. Study of intraop looked at the temporal resolution ability to detect initial dip found that it correlated in length with the length of the afterdischarge.]] [[Surgical human study with electrodes Hbt monophasically increased after electrical discharge, with a more gradual return to baseline (which far outlasted the duration of the afterdischarge).]] [[HBr (deoxygenated Hgb) initially increased for duration of the afterdischarge, then quickly inverted (overshoot) in surrounding areas, which persisted after about a minute beyond the end of afterdischarge) representative of reactive increase in CBF. This may be a novel signal specific to human epileptiform activity (Ma et al, 2009). There may be a long epileptic dip in humans (Zhao et al. 2007 human IOS study; negative BOLD signal consistent with persistent dip Schridde et al. 2008).]] [[In animals, intrinsic optical spectroscopy (IOS) show profound dip at onset of interictal and ictal events.]] [[Microdialysis study (Columbia), shows metabolic response of brain to seizure leads to delayed ICP and lactate/pyruvate response.]] [[ASK SOOJIN // I need help understanding this; is this relevant to include here? -alex]]

3 Investigation Method

To investigate the hypothesis, we collected clinical EEG (cEEG) and LICOX data from eighteen patients with high grade subarachnoid hemorrhage (SAH) or traumatic brain injury (TBI) which resulted in seizures. [[NCC algorithm/protocol??]] [[Table 1]] 7 of the patients had TBI, 11 had aSAH. The mean age of the patients was 54, and the median age was 55. Nine of the 11 SAH patients were female (81.8%), and 4 of 7 of the TBI patients were female (57.1%). Unfortunately, the relative rarity of patients who fit this criteria and who had data available made a large sample size unobtainable.

In this case, because our study sought to discover some link between the brain oxygen data and seizure data we had collected, that our hypothesis might be proven wrong, several [[HOW MANY]] statistical methods of analysis were attempted. [[Selecting appropriate statistical techniques is perhaps the most difficult and important preliminary task.]]

/subsectionSeizure not correlated with LICOX drop below 20

We first examined the probability that a seizure is followed by a LICOX value below 20. If this were the case, there would be a strong association between seizure and low LICOX values. However, examining existing evidence makes this unlikely; examining every seizure as an independent event, we identified the LICOX readings for those seizures an hour, a half hour, and 15 minutes after seizure onset, and associated those seizures with the minimum LICOX value in those time periods.

We did not, however, include any seizures with no LICOX measurements in the intervening time, as this would introduce future error. Only 14.4% of seizures were followed by a LICOX value below 20 within an hour (n = 193), 13.8% were followed by a LICOX value below 20 within 30 minutes (n=123), and 10.3% were followed by a LICOX value below 20 within 15 minutes (n=78). Seizures do not reliably produce a dip below 20 in LICOX values.

Note that error estimates on this data are complicated by the fact that patients often experienced multiple seizures, and LICOX readings for each are likely not independent; that is, seizures that occurred in the same hour might be tagged with the same LICOX reading, and LICOX readings across hours are likely correlated. However,

LICOX readings seem to be uncorrelated over 2 hour spans. Instead of including every seizure, we can include only seizures spaced at least two hours apart, ignoring any intermittent seizures. Using this method, 17.5% of seizures are followed by a Licox value of less than 20 in the next hour, 16.2% in the next 30 minutes, and 12.9% in the next 15 minutes. [[(All three of these values have standard deviations of 6.0 or 6.1). WORK THIS IN]] Interference caused by other seizures should theoretically only lower LICOX values, so these numbers are likely higher than the true values would be, were the seizures completely independent. More applicable to the ICU, we examined the probability that the Licox value dropped below the threshold after the seizure. Including only seizures whose minimum Licox reading in the preceding hour was above 20, we found that only 7.1% (2.0) had a Licox value below 20 in the hour after. That is, only 7.1% crossed the threshold, which would trigger an alarm. Thus, this data powerfully suggests that seizures are rarely followed by a dip in LICOX values sufficient to provoke the traditional ischemic brain oxygen alarm.

We attempted to group seizures by seizure length to examine if longer seizures

caused Licox values to drop more than shorter seizures. We calculated the minimum Licox value in the hour before a seizure subtracting the minimum value in the hour after a seizure; a positive value indicates a rise in the Licox measurement across the seizure. We calculated the mean change, the median change, and the percent of seizures that experienced a drop. None of the values is statistically significant from 0, indicating that seizures seem to not predominantly cause drops in Licox measurements.

	Szr lt 1 min	Szr gt 1 min, lt 5 min	Szr gt 5 min
Mean Change	0.23	-0.68	-0.04
StDeviation	4.3	4.71	5.38
Median Change	0.75	-0.6	-0.5
% that Dropped	0.44	0.53	0.5

3.1 LICOX below 20 not indicative of seizure

The next question we investigated was whether LICOX values below 20 are more likely to be preceded by a seizure. If seizures are unlikely to produce a LICOX value below 20, but a LICOX value below 20 is preceded, with high probability, by a seizure, use of this threshold as an indicator for seizure would still be highly valuable. We found, however, that only 6.3% of LICOX values below 20 were preceded by a seizure in the previous hour, whereas 8.7% of LICOX values above the threshold were preceded by a seizure. Thus, there seems to be no significant difference.

Note that our results are likely incomplete, as we only included patients we identified as having seizures, and did not examine LICOX values of patients unaffected by seizures. However, adding all patients who did not have seizures would only reduce the number of LICOX values below 20 which were preceded by a seizure. Thus, we feel confident that observation of a LICOX value below 20 does not prove a reliable indicator for seizure.

LICOX	Seizure Present	No Seizure Present	%
lt 20	10	148	6.3
gt= 20	91	961	8.7

3.2 LICOX below 20 not indicative of more severe seizures

Finally, we attempted to determine whether LICOX values below 20 might serve as a general indicator of longer seizures. The link between prolonged seizure and poor outcome is well documented [[REF: Status Epilepticus...]], and an indicator of such seizures would still be valuable. We measured the cumulative amount of seizing in the half hour preceding each LICOX value. LICOX values below 20 did not indicate more seizing in the preceding half hour [[IS IT HALF HOUR HERE OR HOUR?]] than LICOX values above the threshold, as the table shows. [[THIS TABLE IS UNCLEAR... DOESN'T MAKE SENSE. WHAT IS .12? IS THIS NORMALIZED? SEEMS VERY UNEVEN]]

Cumulative Seizing in the last 30 minutes:

LICOX	Mean	St Dev
lt 20	0.12	0.56
gt= 20	0.73	5.72

4 Results

Despite many attempts to identify a connection between the traditionally used LICOX threshold and seizure, we found no evidence that seizures were predicted by or correlated with a LICOX drop below 20.

Because we retroactively examined seizure data that had already been collected, we were limited to data that was collected according to the general protocol in the hospital. Thus, LICOX measurements were discrete, not continuous. Additionally, we were only able to procure data for patients we identified as having had a seizure, and the amount of data for each seizure was fairly limited. Though we considered the bias this may have introduced, even under extremely conservative assumptions, we were able to find no support for the idea that seizures can be definitively associated with a brain oxygen drop below 20.

There may yet be utility in monitoring brain oxygen (through LICOX or other methods) in raising clinical suspicion of seizure, if the use of ischemic thresholds is replaced with more sophisticated methods. Seizure does seem to have consistent effect on the variability of brain oxygen; this variability is quantifiable. The utility and usability of the variability measure in a real-time prospective fashion is yet to be determined and should be the focus of future studies.

However, we believe the standard of care involving considering seizure as a possible cause of LICOX drop below 20 is harmful. It may lead caretakers to diagnose seizure more often than is proper, or ascribe more use to the LICOX than is deserved, and leave the LICOX monitor in when it might otherwise be removed.

[[Sidedness: LICOX is Focal, Seizures may be "missed"? Were all data used ipsilateral?]]

5 Future Work

This paper is only a preliminary foray into the area discussed. Future work will include a more thorough study with a larger sample population and more frequent LICOX measurements, and ideally an analysis of the long term trend behavior of the LICOX monitor, with the aim of establishing an accurate seizure detection criteria incorporating observation of the initial dip in brain oxygen, or the recognition of the pattern of dip, followed by recovery. Work must also investigate LICOX's inherently focal nature, and determine whether the sidedness of the seizure might impact such measurement.

We wish to develop such a procedure for utilizing data from the LICOX monitor to detect seizures, and investigate whether incorporation of available patient information, including streaming vital sign data, would improve the accuracy of detection.

The limitations of brain oxygen monitors to detect seizure may be in their threshold-based interpretation. We propose prospective research for more effective strategies of interpreting patient data.