Low brain tissue oxygen predicts poor outcome, but does it give insight to possible interventions?

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Traumatic brain injury (TBI) is the leading cause of death and disability among young adults in North America. Patients with TBI and increased intracranial pressure have a high probability of death or poor outcome (1-3), and this may be due in significant part to secondary brain injury and cerebral ischemia. Thus, in most TBI protocols and guidelines, initial management has centered on the management of intracranial pressure and maintenance of an adequate cerebral perfusion pressure (CPP) to prevent cerebral ischemia and infarction. However, numerous studies have now demonstrated that secondary brain ischemia often occurs in TBI and even in the setting of presumably adequately controlled intracranial pressure and CPP. This indicates that mechanisms other than simple, low global CPP are likely responsible for poor outcome after TBI. More complex metabolic derangements and mitochondrial shutdown are now known to occur in TBI independent of CPP (4).

The recognition of secondary brain hypoxia has led to efforts of monitoring of global cerebral oxygenation by jugular venous oximetry and the development of regional monitoring of brain tissue oxygen tension ($P_{bt}$O$_2$), local cerebral blood flow (CBF), and regional metabolism with microdialysis. In fact, devices to monitor $P_{bt}$O$_2$ were approved by the Food and Drug Administration in 2001. Numerous studies have found that intensity, duration, and number of episodes of low brain $P_{bt}$O$_2$ are associated with poor outcome (5-7). These studies have generally been interpreted as lending credence to
the idea that the brain is highly dependent on a continuous supply of oxygen and glucose to maintain cellular integrity and that low $P_{bt}$O$_2$ is a measure of disruption of this process.

This study by Maloney-Wilensky et al in this issue of Critical Care Medicine is a systematic review of published data on brain tissue monitoring and outcome in severe TBI (8). The authors conclude that low brain tissue oxygen tension ($<10$ mm Hg) for a sufficient duration ($>15-30$ minutes) is associated with poor outcome after severe TBI. In an organized way, this reaffirms that the association of low $P_{bt}$O$_2$ and poor outcome is a robust finding. What remains lacking, unfortunately, is a clear answer to the fundamental question: is this “cause” or is this “effect”? Importantly, they found no significant issues regarding the safety of placement and use of these monitors, suggesting that the real question is one principally of potential benefit, cost, and effort, not risk. The limitations of this study (as acknowledged by the authors) are the low number of included studies, the singular definition of brain tissue hypoxia, and the fact that more than half of the patients came from the same study.

Given the deleterious effects of secondary ischemia after TBI, continuous brain tissue oxygen monitoring is intuitively appealing because it provides an opportunity for detection and intervention. We are convinced that a low $P_{bt}$O$_2$ is associated with a bad outcome. However, to move the field forward it is time to address two issues: what intervention should be undertaken for low $P_{bt}$O$_2$, and does this intervention (or set of interventions) improve patient outcome? Potential interventions to increase $P_{bt}$O$_2$ include increasing the arterial oxygen content through blood transfusion or raising the inspired oxygen concentration (Fio$_2$), or increasing CBF by raising the blood pressure or lowering the intracranial pressure (thereby improving CPP). Unfortunately, there remains no convincing evidence that normobaric hyperoxia can truly improve the overall cerebral oxygen metabolism (CMRO$_2$) after TBI. Initial studies of hyperoxia looked at indirect measures of CMRO$_2$, such as microdialysis, and suggested improved CMRO$_2$ (9). Menzel et al (10) showed a concurrent decrease in tissue lactate in the brain with hyperoxia. However, these studies remain preliminary and are based on physiologic intermediaries, not patient outcome. Despite microdialysis data being promising, a more recent PET study with normobaric hyperoxia demonstrated no improvement in cerebral metabolic rate of oxygen with an increasing Fio$_2$ (11). The possible benefit of hyperbaric hyperoxia in TBI is intriguing but remains understudied (12, 13). Thus, at present, correcting anemia and ensuring optimal saturation of the arterial blood is still the most common method of improving oxygen content of the arterial blood in patients with low $P_{bt}$O$_2$.

In TBI, clinically important mechanisms to ensure adequate brain oxygen delivery include autoregulation of CBF, pressure compensation mechanisms, and CO$_2$ reactivity. $P_{bt}$O$_2$ monitoring allows for the integrity of these mechanisms to be assessed by comparing dynamic and static changes, which occur during regular monitoring or when challenging the system with different interventions such as a rise in Fio$_2$, a temporary increase in mean arterial pressure, or brief hyperventilation. Information from brain
tissue monitoring would then allow for intervention changes targeting CBF and patient autoregulation status (14, 15). Although potentially more appealing mechanistically, this is a much more complex set of interventions than just turning up the \( \text{Fi}_2 \) on the ventilator.

Although initially conceived of as an ischemia monitor, it is now recognized that brain tissue oxygen tension likely represents something more complex and integrative. Rather than total oxygen delivery or \( \text{CMRO}_2 \), \( \text{P}_{\text{bt}} \text{O}_2 \) is more strongly associated with the product of CBF and cerebral arteriovenous oxygen tension difference (\( \text{AVT}_2 \)) (14). Thus, brain tissue oxygen tension is affected more by factors that govern oxygen diffusion rather than total oxygen delivery or \( \text{CMRO}_2 \) (16, 17). Any intervention to be tested must take this into consideration.

Problems also remain as to optimal probe placement location: in the tissue at risk or in the normal brain? Changes in \( \text{P}_{\text{bt}} \text{O}_2 \) correlate well with changes in \( \text{SjvO}_2 \) and correlate with brain positron emission tomography scan when the sensor is placed in noncontused brain, indicating that the sensor is reflecting changes in cerebral oxygenation (18, 19).

This systematic review provides a useful status check regarding where we have been and where we need to go. Monitoring the injured brain is an integral part of the management of patients with severe TBI in modern intensive care units, and metabolic monitoring of brain tissue oxygen tension clearly gives insight into the importance of secondary hypoxic brain injury. The next step is intervention. It is time for randomized clinical trials that target brain tissue oxygen tension as an intermediary, designed to improve patient clinical outcome. However, caution must be considered in determining the intervention to be tested, for it is likely that it is not just the \( \text{P}_{\text{bt}} \text{O}_2 \) number that is important, but rather the underlying physiologic disturbance that it represents that is of greatest importance. It is time to take cerebral metabolic monitoring past its current status as a prognostic tool and make it a guide for intervention.

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