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Hyperoxia – good or bad for the injured brain?

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Abstract

Purpose: For decades it was assumed that cerebral ischemia was a major cause of secondary brain injury in traumatic brain injury (TBI), and management focused on improving cerebral perfusion and blood flow. Following the observation of mitochondrial dysfunction in TBI and the widespread use of brain tissue oxygen tension (PbrO₂) monitoring, however, recent work has focused use of hyperoxia to reduce the impact of TBI.

Recent findings: Previous work on normobaric hyperoxia utilized very indirect measures of cerebral oxygen metabolism (intracranial pressure, brain oxygen tension and microdialysis) as outcome variables. Interpretation of these measures is controversial, making it difficult to determine the impact of hyperoxia. A recent study, however, utilized positron emission tomography (PET) to study the impact of hyperoxia on patients with acute severe TBI and found no improvement on cerebral metabolic rate for oxygen with this intervention.

Summary: Despite suggestive data from microdialysis studies, direct measurement of the ability of the brain to utilize oxygen indicates that hyperoxia does not increase oxygen utilization. This, combined with the real risk of oxygen toxicity, suggests that routine clinical use is not appropriate at this time and should await appropriate prospective outcome studies.

Keywords

head injury; cerebral metabolism; hyperoxia; oxygen

Introduction

Most investigative work in traumatic brain injury (TBI) assumed that cerebral ischemia was a major contributor to brain damage, although some have challenged that assumption. Management traditionally has focused on improving cerebral perfusion and blood flow. However, following the observation of mitochondrial dysfunction in TBI and the widespread use of brain tissue oxygen tension (PbrO₂) monitoring, recent work has focused use of hyperoxia to reduce the impact of TBI.

Ventilation with 100% oxygen raises PbrO₂ in TBI patients and reduces apoptotic cell death in experimental TBI. Microdialysis studies have yielded mixed results and there is considerable controversy how to interpret them. Recent studies with PET indicate that hyperoxia does not improve cerebral oxygen utilization.

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Cerebral metabolism

The brain has an extremely high metabolic rate; its oxygen demand exceeds that of all organs except the heart. Despite its relative small size (2% of total body weight), the brain receives approximately 20% of cardiac output and accounts about 20% the body's oxygen consumption. Energy for metabolism is derived from glycolysis, which takes place in the cytosol, followed by oxidation of the products of glycolysis (pyruvate, lactate) in the mitochondria. Glycolysis produces a net of two high energy phosphates (ATP) per molecule of glucose whereas oxidation of the products yields an additional 34 molecules of ATP. Since it stores no metabolic substrates, the brain requires a continuous supply of glucose and oxygen to maintain its metabolic function.

While both oxygen and glucose are provided by the cerebral circulation, their means of entering the brain are very different. Glucose is moved across the blood-brain-barrier by a complex highly regulated series of transporters while oxygen passively diffuses down its concentration gradient from the blood to the mitochondria. The concentration of glucose in the blood exceeds the amount taken up by the brain by many fold leaving considerable reserve, which protects against the impact of hypoperfusion. On the other hand, blood oxygen content exceeds utilization by only a factor of two or three; thus oxygen supply may be inadequate during periods of hypoperfusion.

Cerebral oxygen delivery

Cerebral oxygen delivery is defined as the product of arterial oxygen content and the regional cerebral blood flow (CBF). Arterial oxygen content (CaO_2) is determined from the sum of oxygen bound to hemoglobin ($\text{Hgb} \times \text{O}_2$ saturation) and oxygen dissolved in the plasma (arterial oxygen tension (PaO_2) $\times$.003). With a normal hematocrit and oxygen tension CaO_2 is approximately 14 vol%. Under physiologic O_2 tensions the amount of oxygen dissolved in plasma is negligible, however, normobaric hyperoxia may increase the amount of dissolved oxygen by ~0.5-1 vol% while hyperbaric oxygen can increase it considerably more. It is also important to recall the hemoglobin dissociation curve, which indicates that hemoglobin is 100% saturated at a PaO_2 of approximately 80 mm Hg. Thus under conditions of normal oxygenation, the two most important factors that influence cerebral oxygen delivery are hemoglobin concentration and CBF.

Cerebrovascular Disturbances in Head Injury

One of the most common findings in the brains of patients who die following TBI is ischemic neuronal damage. (1) However this data must be interpreted cautiously. The population is skewed since the studies only included TBI patients who died as a result of their injury. In addition the pathologic finding could result from reduced cerebral perfusion pressure (CPP), such as increased ICP or systemic hypotension, or could have been iatrogenic, a result of aggressive hyperventilation.

Several approaches have been used to assess for the presence of ischemia in the first few hours after severe TBI. Bouma and colleagues (2;3) defined ischemia as $\text{CBF} < 18 \text{ ml/100g/min}$ and found evidence for ischemia in approximately 1/3 of patients studied within 6 hours of injury. However CBF in that range could result from reductions in metabolism secondary to the injury or sedative administration. Obrist and co-workers (4) found that patients with reduced CBF 1-2 days post injury had reduced CMRO_2 and normal oxygen extraction fraction (OEF), indicating a primary reduction in metabolism, not ischemia. Thus measurement of CBF without concomitant assessment of CMRO_2 and OEF is inadequate to determine the presence or absence of ischemia in TBI.

Sahuquillo and co-workers (5) measured oxygen and lactic acid concentrations in arterial and jugular venous blood in 28 patients with severe TBI. They found that during the first 24 hours after TBI 46% of the patients had a pattern consistent with ischemia based on an elevated lactate-oxygen index (6). However, some caution needs to be exercised in the interpretation of jugular venous lactate levels as they effected by many factors and thus to not necessarily reflect the brain's metabolic state (see below).

An alternative approach used to assess for ischemia uses the arterio-venous difference in oxygen content ($a-vDO_2$). This measure assesses how well CBF and $CMRO_2$ are matched; a relative reduction in CBF to $CMRO_2$ results in a wider $a-vDO_2$. However selection of the appropriate threshold to indicate ischemia is problematic. Normal values for $a-vDO_2$ range from ~4.5 - 9 vol% (7). While an increase in $a-vDO_2$ indicates a relative reduction of CBF in relation to $CMRO_2$, it does not necessarily indicate the cerebral oxygen delivery is inadequate.

In summary, reductions in CBF occur in the first 12 hours following TBI. If cerebral metabolism is normal, the CBF reductions are of a magnitude to indicate ischemia. However measurements of global $CMRO_2$ indicate that metabolism is often suppressed in TBI patients.

Rationale for hyperoxia

As the ability to continuously measure regional brain oxygen tension ($PbrO_2$) in patients became widely available, it was frequently observed that hyperoxia (100% inspired oxygen concentration) led to a rise in $PbrO_2$ (8-10). This observation raised the possibility that increasing the fraction of inspired oxygen (FiO_2) might be beneficial to head injured patients. This possibility has been the subject of considerable study, discussion and controversy. (11; 12) Two alternative hypotheses regarding how hyperoxia might improve brain metabolism in TBI patients have been proposed.

One assumes that oxygen delivery is inadequate and argues that the rise in $PbrO_2$ seen with hyperoxia (13) indicates improved delivery. This theory, however, has limitations. First, as discussed above, it appears that oxygen delivery is adequate in most TBI patients. Second, the increase in arterial oxygen content with normobaric hyperoxia is minimal thus doing little to increase cerebral oxygen delivery. Third, the rise in $PbrO_2$ reflects an increase in partial pressure of oxygen not content. Thus the improvement in $PbrO_2$ seen with hyperoxia does not necessarily indicate improved oxygen delivery.

Alternatively, hyperoxia could improve $CMRO_2$ by improving the brain's ability to utilize delivered oxygen. It is now apparent the mitochondrial function is impaired in head injury patients (14) as well as those with intracerebral hemorrhage. The higher tissue oxygen tension produced by hyperoxia could theoretically improve mitochondrial function and thus oxygen metabolism.

Additionally, the rate of oxygen diffusion is directly proportional to the tension gradient between the vessels and the mitochondria and the conductance through the tissue and the time available for diffusion (15). Endothelial swelling and perivascular edema occur following TBI and require oxygen to travel a longer distance before reaching the mitochondria. An increase in the oxygen tension gradient may facilitate diffusion of oxygen though edematous tissue to reach the mitochondria.

Potential Harm

The harmful effects of hyperoxia have been known for decades. Ventilation with a high fraction of inspired oxygen has been associated with injury to the lens of the eye, lungs, heart, brain and gastrointestinal tract. (16) Hyperbaric oxygen is well known to induce seizures. (17) In the

early 1950s high fraction of inspired oxygen was noted to produce retrolental fibroplasias. Pulmonary toxicity involves damage to the alveolar and epithelium and capillary endothelium producing edema, impaired gas exchange and extensive inflammatory infiltration which can be fatal. (18) Much of the toxicity has been attributed to free radical (reactive oxygen species) formation. Yet, in a rat model of subdural hematoma one study failed to find an increase in free radical formation with hyperoxia. (19)

In addition to toxicity from reactive oxygen species, 100% oxygen can cause cerebral vasoconstriction (20;21) reducing perfusion.

Studies of normobaric hyperoxia in TBI

The impact of hyperoxia on outcome has been studied in a number of experimental models of head injury. In a brain contusion model, produced by the application of negative pressure to the cortex, normobaric and hyperbaric hyperoxia reduced evidence of apoptosis in peri-lesional brain (22).

A number of experimental and clinical studies have investigated the impact of normobaric hyperoxia in TBI. Initial studies that utilized microdialysis to assess the metabolic response in TBI reported reduced lactate levels. (23-25) These data were interpreted to indicate reduced production of lactate due to a shift from anaerobic to aerobic metabolism. However interpretation of lactate levels is far more complex as they may be influenced by a number of factors. CBF determines lactate clearance, independent of production. Thus if CBF were to rise and lactate production was unchanged levels would fall. Furthermore, white blood cells produce lactate. Infiltration by inflammatory cells occurs in TBI (26) and the movement of these cells in and out of the brain could influence lactate levels. Finally lactate may be used as fuel by neurons (27;28) complicating the interpretation of interstitial levels.

Interpreting levels of lactate in relation to pyruvate (lactate/pyruvate ratio) provides an assessment of the brain's redox state. (29;30) Elevated ratios are considered to be indicative of ischemia (31;32) Administration of normobaric hyperoxia to TBI patients has yielded inconsistent results, demonstrating either no change or a fall in the lactate/pyruvate ratio (23; 33). Still these measurements represent only two components of the brain's extraordinarily complex metabolic machinery.

The ability of normobaric hyperoxia to improve brain metabolism has been studied primarily using indirect physiologic measures, the interpretation of which remains disputed. Recently, direct measurement of brain metabolism was performed using PET in a small group of patients with severe TBI (34). Cerebral blood flow, blood volume and CMRO₂ were measured during baseline ventilation with 40% oxygen and again after one hour of ventilation with 100% oxygen. Cerebral metabolic rate for oxygen did not change with hyperoxia indicating that the improved values of PbrO₂, lactate and lactate/pyruvate ratio do not necessarily indicate improved utilization of oxygen.

A recent study compared the impact of 24 hours of 100% oxygen on 52 severe TBI patients to historical control. (33) The groups were matched based on age, sex, post resuscitation GCS and ICP during the first 12 hours post injury. Both groups were monitored with microdialysis and brain tissue O₂ sensors. The results mirror those of previous studies. With hyperoxia ICP was lower, dialysate glucose levels rose, lactate fell and the lactate/pyruvate ratio declined. The magnitude of the difference in ICP is not clinically significant (12 vs. 15 mm Hg) and the implications of the biochemical changes are unknown. None of these changes were seen the normoxia group. At 6 months after injury the mean Glasgow Outcome Score with hyperoxia was higher than in the control group (3.2 compared with 2.8), but these differences were not statistically significant.

Thus the data on the impact of normobaric hyperoxia in TBI almost all use indirect measures of the impact on brain oxygen metabolism. Interpretation of the measures used is controversial an depending on perspective of the interpreter the same data can be said to support or refute improved brain oxygen metabolism with hyperoxia (12). It has been suggested that this controversy could be resolved by direct measurement of cerebral metabolic rate for oxygen with PET or brain high energy phosphates with MRI. Such data are now available in a recent PET study. (34) Patients with acute severe TBI were studied within 24 hours of injury under conditions of stable cerebral perfusion pressure, hemoglobin and arterial pressure of carbon dioxide. Although the number of patients studied was small, the results were consistent: CMRO₂ did not change when inspired oxygen concentration was raised from ~40 to 100% for one hour. These data suggest hyperoxia does not produce the desired effect, increased brain oxygen utilization. They also indicate that indirect measures of oxygen metabolism should be interpreted with caution and cannot reliably predict a change in CMRO₂.

Studies of hyperbaric hyperoxia in TBI

Hyperbaric hyperoxia reduced the inflammatory response (35) and improved outcome in experimental models of head injury. Higher brain ATP levels and improved cognitive performance on the Morris water maze was reported in a rat fluid percussion model. (36) Similarly, in a chronic head injury model, improved performance on the Morris water maze was seen after repeated exposures to hyperbaric oxygen (37).

Two studies by the same group investigated the use of hyperbaric oxygen in severe TBI patients. In one 84 patients were treated with 100% O₂ at 1.5 ATA for 60 minutes every 8 hours for 14 days. (38) Mortality was lower than in controls but functional outcome was no different for the entire cohort, although it appeared to be better in the subgroup with evacuated mass lesions. In a follow-up study (39), 34 patients were grouped into those with low, normal or elevated CBF. In low CBF group, CBF and CMRO₂ rose 1 and 6 hours whereas in those with normal baseline CBF both CBF and CMRO₂ levels were increased at 1 but not 6. While these studies are suggestive, the design and subgroup analyses limit the interpretation of these data.

Conclusions

Normobaric hyperoxia is a simple and appealing approach to the treatment of patients with TBI. Initial enthusiasm developed based on the ability of hyperoxia to improve brain oxygen tension and the availability of clinical tools to continuously measure it. Subsequent studies, however, which used measures more directly related to oxygen metabolism, were equivocal. Recent direct measures of CMRO₂ in TBI patients indicate no benefit. This finding, along with the potential toxicity of hyperoxia, should preclude clinical use of hyperoxia until clear clinical benefit is demonstrated in prospective randomized controlled trials. Limited studies with hyperbaric hyperoxia suggest metabolism may improve, but better studies are needed; it is cumbersome and limited to centers with hyperbaric chambers.

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