Effect of hyperoxia on cerebral metabolic rate for oxygen measured using positron emission tomography in patients with acute severe head injury

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Object. Recent observations indicate that traumatic brain injury (TBI) may be associated with mitochondrial dysfunction. This, along with growing use of brain tissue PO₂ monitors, has led to considerable interest in the potential use of ventilation with 100% oxygen to treat patients who have suffered a TBI. To date, the impact of normobaric hyperoxia has only been evaluated using indirect measures of its impact on brain metabolism. To determine if normobaric hyperoxia improves brain oxygen metabolism following acute TBI, the authors directly measured the cerebral metabolic rate for oxygen (CMRO₂) with positron emission tomography before and after ventilation with 100% oxygen.

Methods. Baseline measurements of arterial and jugular venous blood gases, mean arterial blood pressure, intracranial pressure, cerebral blood flow (CBF), cerebral blood volume, oxygen extraction fraction, and CMRO₂ were made at baseline while the patients underwent ventilation with a fraction of inspired oxygen (FiO₂) of 0.3 to 0.5. The FiO₂ was then increased to 1.0, and 1 hour later all measurements were repeated.

Five patients were studied a mean of 17.9 ± 5.8 hours (range 12–23 hours) after trauma. The median admission Glasgow Coma Scale score was 7 (range 3–9). During ventilation with 100% oxygen, there was a marked rise in PaO₂ (from 117 ± 31 to 371 ± 99 mm Hg, p < 0.0001) and a small rise in arterial oxygen content (12.7 ± 4.0 to 13.3 ± 4.6 vol %, p = 0.03). There were no significant changes in systemic hemodynamic or other blood gas measurements. At the baseline evaluation, bihemispheric CBF was 39 ± 12 ml/100 g/min and bihemispheric CMRO₂ was 1.9 ± 0.6 ml/100 g/min. During hyperoxia there was no significant change in either of these measurements. (Values are given as the mean ± standard deviation throughout.)

Conclusions. Normobaric hyperoxia did not improve brain oxygen metabolism. In the absence of outcome data from clinical trials, these preliminary data do not support the use of 100% oxygen in patients with acute TBI, although larger confirmatory studies are needed.

KEY WORDS • severe head injury • cerebral metabolism • hyperoxia • oxygen tension

O ur understanding of the pathophysiological processes involved in acute brain trauma is evolving. Most investigative work and clinical management of TBI in patients with head trauma had focused on the assumption that secondary cerebral ischemia was a major contributor to ongoing damage, until in recent clinical studies investigators suggested otherwise. Following the observation that severe head injury may be associated with mitochondrial dysfunction and the widespread use of brain tissue PO₂ monitoring, there has been considerable interest in the potential use of hyperoxia to treat patients who have suffered a TBI. It has been proposed that increased oxygen tension, rather than content, may enhance mitochondrial function.

A number of investigators have studied the impact of hyperoxia in models of TBI as well as in patients who have suffered such injuries. In an experimental model of brain contusion, hyperbaric oxygen reduced evidence of apoptotic cell death. Cerebral microdialysis studies in patients with TBI have yielded mixed results. Although there appears to be a consistent increase in brain tissue PO₂ and reduction in lactate levels, the lactate/pyruvate ratio (thought to be a more sensitive index of ischemia) did not change significantly. In one series in which the impact of hyperbaric hyperoxia (100% oxygen at 1.5 atm) on cerebral metabolism was studied, investigators found that in the 15% of patients with reduced CBF, there was a modest improvement in global CMRO₂, 1 and 6 hours after hyperbaric oxygenation. To understand more fully the impact of hyperoxia on cerebral oxygen metabolism following TBI, we used PET to measure directly the global and regional
Effect of hyperoxia on CMRO₂ measured by PET scans after acute TBI

CMRO₂ before and after ventilation with 100% oxygen within 24 hours of injury.

Clinical Material and Methods

Patient Selection and Initial Stabilization

Five unelected patients who had undergone intubation were studied between 12 and 24 hours after acute TBI. All underwent evaluation by members of the neurosurgical and trauma services in the emergency department and were stabilized prior to the PET study. Clinical management of the TBI followed the Brain Trauma Foundation guidelines.¹

After stabilization, ICP monitors were placed in five patients and jugular bulb catheters were placed in four, and informed consent was obtained from family members. Patients were then moved to the PET scanner while undergoing ventilation with an inspired oxygen concentration of 30 to 50%. Baseline measurements of arterial and jugular blood gases, ICP, blood pressure, CBF, CBV, OEF, and CMRO₂ were made. The inspired concentration of oxygen was then increased to 100%, and 1 hour later all measurements were repeated. We chose to repeat our measurements at 1 hour based on the time course in changes in brain tissue PO₂ with hyperoxia that have been reported in the literature.¹¹,¹²,¹³ The inspired oxygen concentration was then reduced to the baseline level, and patients were returned to their rooms.

Patient Cohort

Five patients (three men and two women) were studied at a mean of 17.9 ± 5.8 hours (range 12–23 hours) after trauma. The admission Glasgow Coma Scale score ranged from 3 to 9, with a median of 7. The patients’ mean age was 34 ± 12.2 years (range 18–50 years). Admission computed tomography scans were classified according to the criteria of Marshall et al.¹⁰ as diffuse Type 2 (three patients) and nonevacuated mass lesion (two patients). Values are given as the mean ± standard deviation throughout.

Protocol for PET Studies

All patients were studied using a CTI ECAT EXACT HR 47 PET scanner (Siemens) located in the Neurology/Neurosurgery Intensive Care Unit. Each scan was acquired in the two-dimensional mode, and images were reconstructed with filtered back projection by using measured attenuation and scatter correction and then filtered with a Gaussian filter to a resolution of 16.3 mm full width at half maximum. The PET scanner was calibrated for conversion of PET counts to quantitative radiotracer concentrations as previously described.¹⁵ Arterial blood was sampled and the arterial time/activity curve was determined using a scintillation counter.

Regional CBF was measured using an adaptation of the Kety autoradiographic method with a bolus injection of ¹⁵O-labeled water.²⁵ Regional CBV was measured using brief inhalation of ¹³O-labeled carbon monoxide. Regional CMRO₂ and OEF were calculated using the CBF and CBV measurements and inhalation of ¹⁵O-labeled oxygen.¹³ Quantitative measurements of CaO₂ were performed with an oxygen fuel cell (LEXO2CON-K; Hospex Fiberoptics). This instrument measures the total of both hemoglobin-bound and plasma-dissolved oxygen in blood.

Processing of PET Images: Bihemispheric Data

Each patient’s PET images were aligned with one another using Automated Image Registration software (AIR; provided by Roger Woods, University of California, Los Angeles).²⁶ An image mask was created that comprised the brain above the cavernous sinus, below the superior sagittal sinus, and excluding large vessels visible in the CBV image. Bihemispheric CBF, CBV, CMRO₂, and OEF data measured at baseline and during 100% oxygen ventilation were calculated using this image mask.

Statistical Analysis

Changes in physiological and bihemispheric PET variables before and during ventilation with 100% oxygen were compared using paired t-tests. Because the primary hypothesis was that ventilation with 100% oxygen would increase CMRO₂, a probability value of 0.05 was used as the criterion for statistical significance for this comparison. For most variables two-tailed tests were used; however, one-tailed tests were used for PO₂ and oxygen content because they would not be expected to fall with an increase in FiO₂. Probability values were calculated for the other comparisons and are reported, although assigning statistical significance is problematic because of the multiplicity of comparisons and the correlations among the different variables.

Results

Table 1 shows the physiological data before and during ventilation with 100% oxygen. As expected, there was a marked rise in PaO₂ (p < 0.0001) and a small rise in CaO₂ (p = 0.03). There were no significant changes in systemic hemodynamic or other blood gas measurements. During ventilation with 100% oxygen, there was no change in bihemispheric CMRO₂ (Table 2). In the two patients who had CBF values that would have been classified as low by Rockswold et al.¹⁹ in their study of the impact of hyperbaric hyperoxia on CMRO₂, the CMRO₂ decreased slightly, from 0.85 to 0.69 ml/100 g/min in one and from 2.00 to 1.70 ml/100 g/min in the other.

Discussion

The ability of hyperoxia to improve cerebral metabolism has been the subject of considerable study, discussion, and controversy.³,⁸ To date, the ability of normobaric hyperoxia to improve brain metabolism has been studied using only indirect physiological measures, the interpretation of which remains disputed. We present here the first data directly measuring CMRO₂ following ventilation with 100% oxygen in patients with acute TBI, and found that hyperoxia increased PaO₂ and CaO₂ but had no impact on the brain’s consumption of oxygen.

Two alternative hypotheses regarding how hyperoxia might improve brain metabolism in patients with TBI have been proposed. In one it is assumed that oxygen delivery is inadequate following TBI, and it is argued that the rise in brain tissue PO₂ seen with hyperoxia²⁵ indicates improved delivery. This theory, however, has limitations. First, it is not clear that oxygen delivery is inadequate in patients with TBI. Measurements of the OEF with PET,¹ and of the jug-
ministration of 100% oxygen to patients with TBI, however, has yielded inconsistent results demonstrating either a reduction or no change in the lactate/pyruvate ratio. Additionally, these values represent only two small pieces of the extraordinarily complex metabolic process of the brain. Direct measurement of brain oxygen consumption bypasses the complex interpretation of microdialysis data, providing direct quantitative assessment of the brain’s use of oxygen. If hyperoxia improves mitochondrial function, then CMRO₂ will rise. Our data do not show this response, indicating no measurable metabolic effect of normobaric hyperoxia.

This study has several important limitations. No patients were studied fewer than 12 hours after injury, hyperbaric oxygen was not tested, and CMRO₂ was only measured after 1 hour. Thus we cannot exclude the possibility that a more robust response would be seen at a later point.

**Conclusions**

Although the number of patients we studied was very small, there was not even a hint of a consistent improvement in brain oxygen metabolism. Of course, we cannot rule out the existence of an individual patient who may respond differently; this is an issue that could be addressed with larger studies. Nevertheless, these results do not support the use of 100% oxygen in patients with TBI based on the rationale that it generally improves brain oxygen metabolism.

**Disclaimer**

None of the authors has any relevant conflicts.

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