

REVIEW ARTICLES

Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity[†]

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There has long been an appreciation that cerebral blood flow is modulated to ensure adequate cerebral oxygen delivery in the face of systemic hypoxaemia. There is increasing appreciation of the modulatory role of hyperoxia in the cerebral circulation and a consideration of the effects of such modulation on the maintenance of cerebral tissue oxygen concentration. These newer findings are particularly important in view of the fact that cerebrovascular and tissue oxygen responses to hyperoxia may change in disease. Such alterations provide important insights into pathophysiological mechanisms and may provide novel targets for therapy. However, before the modulatory effects of hyperoxia can be used for diagnosis, to predict prognosis or to direct therapy, a more detailed analysis and understanding of the physiological concepts behind this modulation are required, as are the limitations of the measurement tools used to define the modulation. This overview summarizes the available information in this area and suggests some avenues for further research.

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One of the prime purposes of cerebral perfusion is to ensure oxygen delivery to the brain. Cerebral blood flow (CBF) is coupled to cerebral oxygen metabolism to ensure appropriate oxygen delivery both at baseline and dynamically in response to cortical activity. There has long been an appreciation that CBF is modulated to ensure adequate cerebral oxygen delivery in the face of systemic hypoxaemia.^{6 28 43} There is increasing appreciation of the modulatory role of hyperoxia in the cerebral circulation and a consideration of the effects of such modulation on the maintenance of cerebral tissue oxygen levels.^{59 82} These newer findings are particularly important in view of the fact that cerebrovascular and tissue oxygen responses to hypoxia and hyperoxia may change in disease. Such alterations provide important insight into pathophysiological mechanisms and may provide novel targets for therapy. However, before the modulatory effects of hyperoxia can be used for diagnosis, to predict prognosis or to direct therapy, a more detailed analysis and understanding of the physiological concepts behind the modulation is required, as are the limitations of the measurement tools used to define the

modulation. This review summarizes the available information in this area and suggests some avenues for further research.

Cerebral oxygen vasoreactivity

Cerebrovascular responses to hypoxia

Many factors influence CBF, including oxygen, carbon dioxide, metabolic demand and blood pressure. The classical response of CBF to changes in the arterial partial pressure of oxygen (Pa_{O_2}) is shown in Figure 1.

Over a normal physiological range of Pa_{O_2} (7–13.33 kPa), there is little change in CBF. This is because CBF is related

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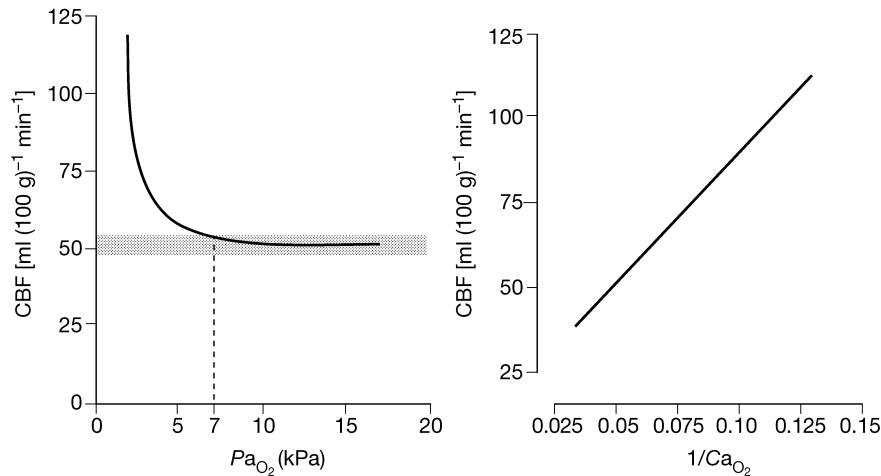


Fig 1 The influence of arterial oxygen content (Ca_{O_2}) and arterial partial pressure of oxygen (Pa_{O_2}) on cerebral blood flow (CBF). Below Pa_{O_2} ~7 kPa (53 mm Hg), CBF increases. Within a normal physiological range of Pa_{O_2} there is little change in CBF (shaded box). Adapted with permission.⁴³

to the arterial content of oxygen (Ca_{O_2}) rather than Pa_{O_2} , and the shape of the haemoglobin–oxygen dissociation curve means that Ca_{O_2} is relatively constant over this Pa_{O_2} range. Hypoxaemia, however, is a potent stimulus for arterial dilatation, CBF beginning to increase at a Pa_{O_2} of ~7 kPa (53 mm Hg); a decrease in the Pa_{O_2} from 6.67 to 3.33 kPa (50 to 25 mm Hg) will produce cerebral vasodilatation sufficient to double the CBF. Despite the fact that it is a fundamental and widely discussed response, data on the precise threshold at which hypoxic vasodilatation occurs are limited. The conventional thresholds quoted above arise from experimental work done in anaesthetized dogs in the 1960s.⁵⁴ More recent work in awake volunteers suggests that hypoxic vasodilatation may be triggered at Pa_{O_2} levels as high as 7.9 kPa (60 mm Hg).²⁸ The mechanisms responsible for this increase have been investigated extensively; hydrogen ions, potassium ions, adenosine, nitric oxide, arachidonic acid metabolites and ATP-sensitive K^+ channels have all been implicated as mediators of the process.⁷⁷ Although clinical data from patients with chronic anaemia appear to relate CBF to Ca_{O_2} rather than Pa_{O_2} ,⁶ the situation may be different with acute hypoxaemic challenges and, at least in rodents, the Pa_{O_2} appears to be more important than the arterial oxygen content in regulating cerebral vascular tone.⁷⁷

Cerebrovascular responses to hyperoxia

The response of CBF to hyperoxia ($Pa_{O_2} >15$ kPa, 113 mm Hg), the cerebral oxygen vasoreactivity (COVR), is less well defined. Kety and Schmidt originally described, using a nitrous oxide washout technique,⁴⁵ a reduction in CBF of 13% and a moderate increase in cerebrovascular resistance in young male volunteers inhaling 85–100% oxygen.⁴⁶ Subsequent human studies (Table 1), using a

variety of differing methods, have also shown CBF reductions with hyperoxia, although the reported extent of this change is variable.^{2 50 59 61 62 64 67 84} Omae and colleagues⁶⁴ assessed how supra-atmospheric pressures influenced CBF, as estimated by changes in middle cerebral artery flow velocity (MCAV) in healthy volunteers. Atmospheric pressure alone had no effect on MCAV if Pa_{O_2} was kept constant. Increases in Pa_{O_2} did lead to a significant reduction in MCAV; however, there were no further reductions in MCAV when oxygen was increased from 100% at 1 atmosphere of pressure to 100% oxygen at 2 atmospheres of pressure. This suggests that the ability of the cerebral vasculature to constrict in response to increasing partial pressures of oxygen is limited. Although hyperbaric oxygen is thought to increase CBF in head-injured patients, when the CBF is measured before and after the period of hyperbaric oxygen; however, the acute response of CBF to hyperbaric oxygen after head injury is not known.⁶⁶

Some of the differences between the studies may result from the varying methods used to measure CBF, each with its own advantages and disadvantages, effects on physiology, limits to the level of inspired oxygen achievable, and ability to determine changes in regional and global CBF. A full description of the different techniques is beyond the scope of this review, but the various techniques are summarized in Table 2; interested readers are directed to recent reviews on the subject.^{7 43 56 74} Differences in respiratory physiology mean that there will be inter-individual differences in Pa_{O_2} for a given inspired fraction of oxygen ($F_{I_{O_2}}$). It would therefore seem more logical to quantify changes in CBF in terms of changes in Pa_{O_2} rather than $F_{I_{O_2}}$. As carbon dioxide usually has a much more dramatic effect on CBF than oxygen, any measurement of COVR requires strict control of carbon dioxide or, at least, correction of CBF to take into account changes in carbon dioxide.

Table 1 COVR studies

Study	Patients/subjects	Method	Results	Comments
Kety and Schmidt, 1948 ⁴⁶	Six healthy males	Nitrous oxide. Oxygen increased from 21% to 85–100%	Significant decrease of 13% in mean cerebral blood flow	
Leahy <i>et al.</i> , 1980 ⁵⁰	12 preterm infants	Based on measurement of occipitofrontal circumference during inspiration of 100% oxygen	15% reduction in CBF	Hyperventilation during hyperoxia was corrected for by adding 1–2% CO ₂ to inspired gas. The method of CBF measurement is only suitable for young infants
Nakajima <i>et al.</i> , 1983 ⁶¹	49 healthy volunteers. 38 asymptomatic volunteers with risk factors for cerebral arteriosclerosis. 25 patients with vertebrobasilar insufficiency. 37 patients with unilateral hemispheric infarctions	¹³³ Xe inhalation followed by clearance. Oxygen increased from 21% to 100%	Mean reduction in CBF of 10.8%. Reduction of 16.2% in normal subjects younger than 50 yr with symmetrical hemispheric reductions. Lower CBF reductions in patients with risk factors, vertebrobasilar insufficiency and hemispheric infarction. In acute infarction there was paradoxical change in CBF, with flow increasing rather than decreasing in the infarcted hemisphere	Only grey matter flow was assessed. There were significant reductions in E'_{CO_2} during hyperoxia but this was not enough to account for the changes in CBF
Amano <i>et al.</i> , 1983 ²	84 healthy volunteers. 11 patients with Alzheimer's type dementia. Eight patients with MID	¹³³ Xe inhalation followed by clearance. Oxygen increased from 21% to 100%	Progressive decrease in COVR with advancing age. No significant difference in COVR between patients with Alzheimer's dementia and age-matched controls. Patients with MID showed reduced COVR; COVR was asymmetrical between hemispheres and heterogeneous within hemispheres	Only grey matter flow was assessed. Significant reduction in E'_{CO_2} during hyperoxia, but not enough to account for the changes in CBF.
Nijima, 1988 ⁶²	15 full-term infants. 17 premature infants	Anterior cerebral artery blood velocity using Doppler. Oxygen increased to produce a 3-fold increase in arterial PO_2	Reduced vasoreactivity in premature infants compared with full-term infants. In premature infants velocities remained decreased, on return to normoxia, during the 10 min observation period. Velocities rapidly returned to normal in full-term infants	Significant falls in CO ₂ during hyperoxia in the full-term infants, which contributed to most of the reduction in flow velocity. This was not the case for the premature infants
Rostrup <i>et al.</i> , 1995 ⁶⁷	Six healthy volunteers	Magnetic resonance phase-contrast angiography. Oxygen increased from 21% to 50% and 100%	27% reduction in CBF during inhalation of 100% oxygen, no flow changes during moderate changes in F_{IO_2}	Magnetic resonance phase-contrast angiography quantifies flow in the major cerebral arteries but gives no information about regional changes. No significant changes in CO ₂
Omae <i>et al.</i> , 1998 ⁶²	Eight healthy volunteers	MCAFV using transcranial Doppler. Oxygen increased from 21% to 100%	20% reduction in velocities	Only MCAFV was assessed. In a further part of the study, high atmospheric pressure <i>per se</i> (PO_2 kept constant) did not influence CBF in humans; CO ₂ stability was good
Menzel <i>et al.</i> , 1999 ⁵⁹	Six patients with severe head injury	Xe-CT scan at 35% oxygen and 60% oxygen	Average global decrease in CBF of ~9%. Extent of vasoreactivity response depended on baseline regional CBF	Time of the study in relation to injury is not recorded. 30% Xe was administered by inhalation; it was therefore impossible to give 100% oxygen
Watson <i>et al.</i> , 2000 ⁸⁴	12 healthy volunteers	Magnetic resonance phase-contrast angiography and 100% oxygen	Mean decrease in CBF of >20%, greater in younger than in older subjects. Decrease in CBF was maintained during hyperoxia and returned to normal, after discontinuation of hyperoxia, over ~6 min	There were significant reductions in measured E'_{CO_2} . This may be methodological and does not account fully for the changes found in CBF

CBF=cerebral blood flow, COVR=cerebral oxygen vasoreactivity, CT=x-ray computed tomography, CTOR=cerebral tissue oxygen reactivity, E'_{CO_2} =end-tidal carbon dioxide, F_{IO_2} =inspired fraction of oxygen, FV=flow velocity, GOS=Glasgow Outcome Score, MCA=middle cerebral artery, MCAFV=middle cerebral artery flow velocity, MID=multi-infarct dementia, MRI=magnetic resonance imaging, N₂O=nitrous oxide, PO_2 =partial pressure of oxygen, ^{99m}Tc HMPOA=technetium 99m hexamethylpropyleneamineoxime, Xe=xenon.

Table 2 Measurement of cerebral blood flow

Technique	Method	Comments
Kety–Schmidt ⁴⁵	Uses rate of uptake of N ₂ O to measure global CBF	Cumbersome and invasive. Requires jugular bulb and arterial catheters. Overestimates low perfusion states. N ₂ O is not a truly inert tracer. The technique can be carried out using inert tracers such as krypton 85 and argon 25. Global measurement
¹³³ Xe washout	Classic method uses extracranial gamma sensors to measure washout curve of radioactive Xe after intracarotid injection. Summated curves show fast and slow washout components (? grey and white matter). Modifications include i.v. and inhalational administration	Predominantly a measure of cortical blood flow. Limited spatial resolution. Recirculation and contamination by extracranial tissues may affect results. Regional CBF reductions on one side may be missed because of activity sensed in deeper or contralateral tissues. Regional measurement
Xe-CT	Stable Xe is radiodense and leads to enhancement of tissue on standard CT scans. Cerebral perfusion can be calculated from the time course of the build up of radiodensity	Signal-to-noise ratio can be high. Even low concentrations of Xe (30%) may influence CBF. Regional measurement
Doppler ultrasonography	Measures FV in the major cerebral vessels, most commonly the middle cerebral artery	Non-invasive. FV is an indirect measure of CBF. Use of FV to assess changes in CBF relies on stability of both the angle of insonation and the diameter of the insonated vessel. Regional measurement
Phase-contrast magnetic resonance angiography	Directional magnetic gradients are used to induce velocity-dependent phase shifts in the MR signal from blood. Knowledge of the cross-section of the vessel and calculated flow velocity from this technique allows estimation of large-vessel blood flow	Measure of CBF but not perfusion. Only a measure of flow in large vessels (e.g. carotids), therefore poor spatial resolution
MRI	Dynamic tracking of a bolus of a paramagnetic contrast agent or arterial spin labelling	Quantification is difficult
Positron emission tomography	Positrons collide with electrons, resulting in destruction of both and emission of two photons travelling in opposite directions. A large number of detector pairs are used to construct regional radioactivity. ¹⁵ O-labelled water (H ₂ ¹⁵ O), given as a bolus or using a steady-state technique, can be used to quantify regional cerebral perfusion	¹⁵ O has a short half-life and therefore repeated measurements are possible. Coregistering with conventional CT or MRI images can enhance the spatial resolution. Expensive and technically demanding equipment. Arterial blood sampling required.
Single photon emission computed tomography (SPECT)	A gamma emitter, ^{99m} Tc HMPOA, is most commonly used. Injected i.v. and distributed similarly to CBF. Rotating or multidetector gamma camera used	Radiotracers have a long half-life that makes repeated measurements difficult. Quantitative measurements of CBF have not been very successful
Thermal diffusion	A probe is inserted into the brain through a burr hole. Local cortical blood flow is calculated from the temperature difference between two plates or from the tissue's ability to dissipate heat	Invasive. Continuous. Only local, cortical blood flow measured

FV=flow velocity, MR=magnetic resonance. For other abbreviations see footnote to Table 1.

While the physiological purpose of hypoxaemic vasodilatation is clear (maintenance of cerebral oxygen delivery), the reasons for hyperoxic vasoconstriction are less obvious. One hypothesis suggests that COVR is a mechanism by which the brain attempts to protect itself against high partial pressures of oxygen, perhaps to limit the production of oxygen free radicals. Pulmonary and central nervous system oxygen toxicity are well described in both animals and humans, and both are believed to result from excess production of reactive oxygen species and disinhibition of the transcription factor nuclear factor- κ B (nuclear factor- κ B has important proinflammatory activity).^{9–11 13} Central nervous system oxygen toxicity is a well-recognized problem in divers when exposed to oxygen pressures >160 kPa (1200 mm Hg), leading to convulsions and loss of consciousness, usually without any warning symptoms. It is interesting that hypercapnia lowers the threshold for central nervous system oxygen toxicity, probably because of vasodilatation and therefore increased exposure to oxygen. In rats, the central nervous system toxicity may result from nitric oxide-induced escape from oxygen-induced

vasoconstriction and thus exposure of tissues to excessive oxygen.¹⁴

Cerebral vasoreactivity in clinical settings

Three studies have looked more specifically at the effects of pathology on COVR (Table 1). Nakajima and colleagues⁶¹ showed that COVR is reduced in patients with risk factors for cerebral arteriosclerosis, vertebrobasilar insufficiency and hemispheric infarction. In fact, in acute infarction there was a paradoxical change in CBF, flow increasing rather than decreasing in the infarcted hemisphere. Amano and colleagues² showed reductions in COVR with age, and showed that COVR is reduced and more heterogeneous in patients with multi-infarct dementia than in age-matched controls. These studies suggest that there has been disruption of the normal ability of the cerebral vasculature to constrict in the presence of high levels of arterial oxygen. Both studies used an inhalation xenon 133 (¹³³Xe) washout technique for determining CBF, a technique that is most

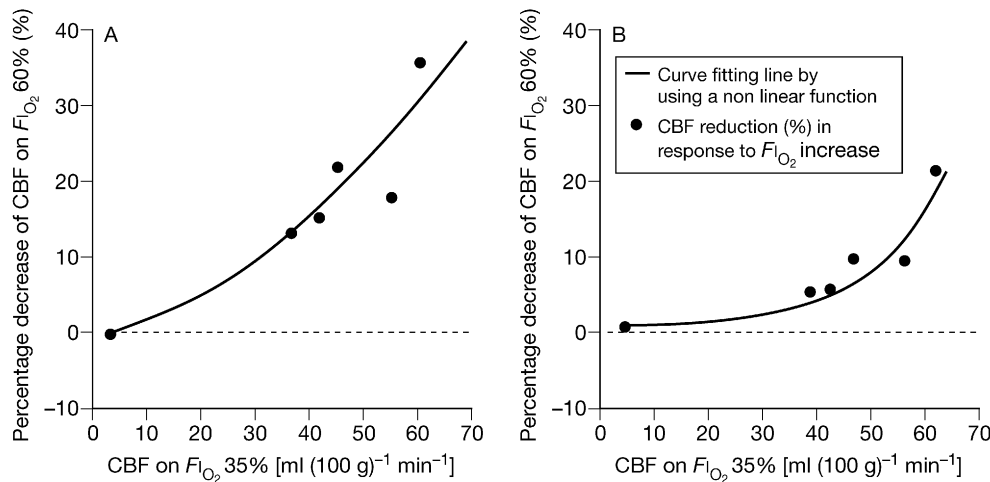


Fig 2 Non-linear curve-fitting regression model between cerebral blood flow (CBF) on 35% inspired oxygen ($F_{I_{O_2}}$) and the percentage decrease in CBF on 60% oxygen in a sequential double CBF study in six patients with severe traumatic brain injury. (A) CBF changes in a region of interest in the right frontal lobe that appeared to be normal on CT scan. (B) Global CBF changes. Adapted with permission.⁵⁸

suiting to measurement of cortical blood flow and provides little information about the white matter compartment.⁵⁶ The use of several regional detectors placed over each cerebral hemisphere gives a certain amount of information on regional perfusion, although precise anatomical correlations, and comparisons of the same region from one study to another, are only semiquantitative. Menzel and colleagues⁵⁹ used stable xenon computed tomography (CT) to determine COVR, which makes use of the fact that stable xenon is radiodense, and therefore CBF can be calculated from the time course of tissue build-up of radiodensity. They demonstrated a mean reduction in CBF of approximately 9%, with an increase in inspired oxygen from 35 to 60%, in six patients with severe traumatic brain injury. The same group also assessed the response of CBF to hyperoxia in an undamaged region of interest in the right frontal lobe, and found an average reduction in CBF of 19.3%. Both globally and in the region of interest, the extent of the COVR was found to depend on the level of the baseline regional CBF (Fig. 2). It is difficult to draw firm inferences from Menzel's work as only six patients were studied, one of whom had negligible CBF, but it does serve to demonstrate the paucity of human data regarding traumatic brain injury and COVR.

COVR has not been compared with other measures of cerebral vascular reactivity, such as carbon dioxide reactivity (changes in CBF in response to changes in P_{aCO_2}) and pressure autoregulation, both of which are known to be prognostic indicators after traumatic brain injury.^{12 53 63 70 73} Therefore, it is not known whether COVR is a measure of vascular reactivity *per se* (irrespective of the stimulus) or whether the cerebrovascular response to oxygen is important in itself. Such comparisons probably need to be preceded by a better understanding of the physiology and a firmer methodological base.

Cerebral tissue oxygen partial pressures

Physiological premises

Measurement techniques

Several different types of tissue gas analysis probes are available which are capable of measuring the partial pressure of oxygen (P_{tO_2}) within a tissue of interest. The volume of tissue sampled by these sensors is probably only in the order of a few cubic millilitres.³⁰ Although there is some uncertainty over the exact characteristics of the partial pressures that tissue sensors measure, for example whether recordings are representative of intracellular or extracellular gas pressures, and the influence of sensor position in relation to capillaries and arterioles, P_{tO_2} is most probably a measure of extracellular oxygen tension and thus reflects the balance between oxygen supply and tissue demand. In metabolically active tissue, an oxygen concentration gradient exists from the arterial to the venous ends of a capillary as a result of oxygen extraction. Normally it is assumed that there is a minimal oxygen gradient between the extracellular space and the end-capillary compartment, and thus that P_{tO_2} reflects end-capillary oxygen tension. This may not be the case after a severe head injury, when large end-capillary—tissue oxygen gradients occur, probably reflecting endovascular oedema or microscopic arteriovenous shunts.²⁷

Cerebral tissue oxygen partial pressures (P_{bO_2}) can be measured using one of the two commercially available sensors. The Licox system (GMS, Kiel-Mielkendorf, Germany) consists of a sensor that includes a polarographic Clark-type electrode, and a thermocouple for temperature measurement. The electrode consumes tiny quantities of the available tissue oxygen in an electrochemical reaction that produces an electrical signal that is proportional to P_{bO_2} . The Neurotrend™ system (Codman, Raynam, MA, USA) is made up of four different sensors (temperature, P_{bO_2} , P_{bCO_2} ,

and pH) staggered over approximately 2 cm. The oxygen sensor consists of a fibre in which the holes are filled with silicone rubber that contains entrapped ruthenium-based dye. Blue light at 450–470 nm is passed down the fibre and is absorbed by the dye. The dye emits a proportion of the energy it has absorbed as light of wavelength 620 nm. However, in the presence of oxygen, the amount of this fluorescent light is reduced (so-called oxygen quenching). The amount of quenching is proportional to the concentration of oxygen and thus, if the amount of fluorescent light is measured, an estimate of Pb_{O_2} can be made. Both sensors are approximately 0.5 mm in diameter but the oxygen-sensing areas are of different lengths; both can be implanted directly into brain tissue. The accuracies of the two sensors are quoted at between 0.1 and 0.5 kPa (1–3.5 mm Hg), but their accuracy declines when oxygen levels are supra-physiological. The two sensors have never been compared in a clinical situation. Before the Neurotrend sensor was developed, a Paratrend sensor (Codman) was used in some studies;^{58, 59} early models of the Paratrend used a modified Clark electrode to measure oxygen partial pressure, but more recently oxygen-quenching technology has been introduced. The Clark electrode Paratrend has been compared *in vivo* with the Licox, with various reports on the comparability between the two sensors.^{68, 79} The Paratrend sensor is designed for arterial blood gas monitoring. It is calibrated to work at higher oxygen tensions and therefore may be more accurate in the measurement of supranormal oxygen levels.

Several other monitoring tools and imaging techniques are available to assess cerebral oxygenation, including jugular bulb oximetry, microdialysis parameters, near infrared spectroscopy and positron emission tomography with ^{15}O ; detailed descriptions of these techniques are beyond the scope of this review. Interested readers are directed to recent reviews on the subject.^{29, 41}

Normal values and modulators

Few data exist on normal values of Pb_{O_2} in humans.⁸² In cats and dogs, normal values have been reported at 3.7 (SD 0.9) kPa [28 (7) mm Hg].⁵² Values of 4.3–4.7 kPa (32–36 mm Hg) have been reported in normal tissue in three patients undergoing brain tumour surgery,⁴ and values of 3.4–13.7 kPa (25–104 mm Hg) were reported in seven patients having elective clipping of intracranial aneurysms.¹⁵ The variability in these figures may be explained in part by variations in the factors determining brain tissue oxygen, which are outlined below.

Cerebral blood flow. There is conflicting evidence as regards the relationship between Pb_{O_2} and CBF. Menzel and colleagues⁵⁹ and Doppenberg and colleagues¹⁶ have used a single stable xenon-CT scan to measure CBF in a region of interest around a Paratrend probe and have found reasonable correlations with Pb_{O_2} . However, Gupta and colleagues²⁷ did not find a significant correlation between

CBF and Pb_{O_2} , using a Neurotrend sensor to determine Pb_{O_2} and $H_2^{15}O$ positron emission tomography imaging to determine CBF. All of these studies were in brain-injured patients.

Cerebral perfusion pressure. After traumatic brain injury, episodes of reductions in cerebral perfusion pressure (CPP) undoubtedly contribute to reductions in Pb_{O_2} , various thresholds for CPP having been reported.^{1, 3, 47, 49} Kiening and colleagues⁴⁹ were able to show a third-order regression correlation between Pb_{O_2} and CPP when a Licox sensor was inserted into non-injured frontal tissue.

Pa_{CO_2} and Pa_{O_2} . In most head-injured patients, hyperventilation results in a decrease in Pb_{O_2} when the sensor is placed in an uninjured part of the brain,^{26, 37} although increases are more commonly seen when the sensor is in an area of pathology.²⁶ Various studies have shown that episodes of hypoxaemia may contribute to reductions in Pb_{O_2} .^{1, 49, 82} The changes in Pb_{O_2} in response to hyperoxia are discussed below (see Cerebral tissue oxygen reactivity).

Ischaemia. Imbalances between metabolic demand and supply will lead to increases in oxygen extraction fraction and thus to reductions in end-capillary oxygen tension. Tissue oxygen levels should therefore reflect changes in oxygen supply–demand relationships. Although some correlations have been found between Pb_{O_2} and other indicators of ischaemia, such as jugular venous oxygen saturation (Sj_{O_2})^{23, 26, 37, 49} and regional lactate levels,⁷⁸ a poor correlation was found between Pb_{O_2} and end-capillary oxygen tension, as calculated from ^{15}O positron emission tomography data.²⁷ Poor correlations are not necessarily surprising, as differences in the mechanisms of ischaemia and the ischaemic burden will influence different monitoring modalities in different ways, as will the compartment from which the measurement is made. Ischaemic thresholds for Pb_{O_2} have been variably described using a number of different approaches, such as outcome analysis after head injury,^{5, 16, 17, 47, 59, 79, 81, 85} relating Pb_{O_2} to recognized threshold limits for CBF,^{17, 59} relating Pb_{O_2} to Sj_{O_2} limits,⁴⁹ assessing Pb_{O_2} in patients with a compromised cerebral circulation,³¹ and assessing thresholds for infarction during cerebral aneurysm clipping.⁴⁴ The threshold for ischaemia that is most commonly used is approximately 1.3 kPa (10 mm Hg).

Pharmacological and pathological modulation of $CMRO_2$. If flow–metabolism coupling is intact, changes in the cerebral metabolic rate of oxygen ($CMRO_2$) should not result in changes in Pb_{O_2} . However, normal coupling of CBF is only retained in 45% of comatose head-injured patients,⁶³ and pharmacological manipulation of $CMRO_2$ may also disrupt normal coupling. Two studies have suggested that etomidate can lead to reductions in Pb_{O_2} , sometimes to levels considered ischaemic;^{19, 32} this is

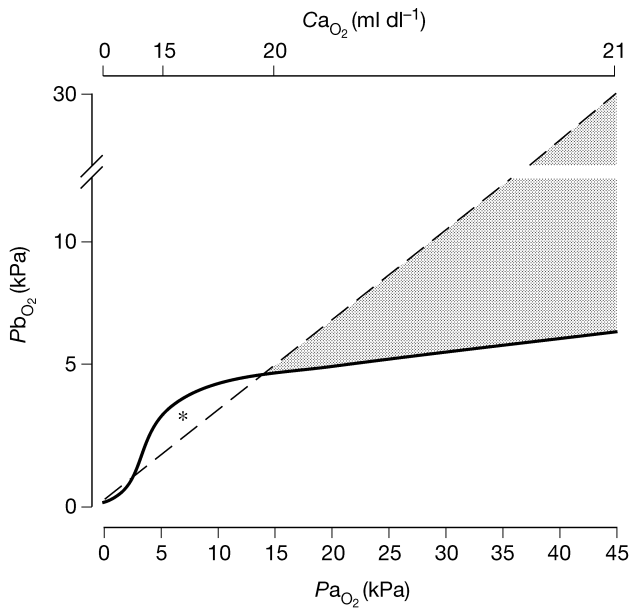


Fig 3 Two hypothetical models of the relationships between brain tissue oxygen (Pb_{O_2}) and arterial oxygen content (Ca_{O_2}) (solid line) and between Pb_{O_2} and arterial partial pressure of oxygen (Pa_{O_2}) (dashed line). Hyperoxia ($Pa_{O_2} > 15$ kPa) is indicated by the shaded area; within this region the relationship does not fit either model but falls between the two (see text). Note the non-linear Ca_{O_2} axis. *There are very little data to support either model under hypoxic conditions.

probably a result of a reduction in oxygen supply attributable to vasoconstriction, which is over and above the reduction in metabolic oxygen requirements. Desflurane has the opposite effect, with increases in Pb_{O_2} as inhaled desflurane increases from 3% to 9%, probably as a result of vasodilatation and hyperaemia. Pb_{O_2} falls with a reduction in temperature, the fall becoming significant at a brain temperature below 35°C.²⁵ This reduction in Pb_{O_2} is associated with increases in Sj_{O_2} and therefore may represent a change in oxygen off-loading at the capillary level as the oxygen dissociation curve shifts to the left. Mitochondrial dysfunction will result in impaired ability to utilize oxygen and a low $CMRO_2$, and could arguably result in vasodilatation; consequently Pb_{O_2} will be raised. This constellation of findings would seem plausible in mitochondrial dysfunction, but has not been confirmed by robust experimental data in humans or experimental models.

Cerebral tissue oxygen reactivity

The expected changes in Pb_{O_2} that occur with changes in Pa_{O_2} [cerebral tissue oxygen reactivity (CTOR)] are not immediately intuitive. If brain tissue oxygen were dependent on arterial oxygen content, then, because of the shape of the oxygen dissociation curve, one would expect to see little change in Pb_{O_2} during normoxia and hyperoxia. If brain tissue oxygen were dependent on Pa_{O_2} , one would expect changes in Pa_{O_2} to be exactly reflected by changes in Pb_{O_2} . In practice, changes in Pb_{O_2} with changes in Pa_{O_2} do

Table 3 Difficulties in measurement of normal CTOR

Invasive brain tissue monitors required, e.g. Neurotrend
Measurements of tissue oxygen are very local and may not fully reflect global heterogeneity
Probe insertion normally requires general anaesthesia, which may have independent effects on tissue PO_2
For ethical reasons, human subjects can only have brain tissue oxygen monitoring if there is an ongoing pathological process

not fit either of these models. The experimental evidence suggests that Pb_{O_2} increases with an increase in Pa_{O_2} , but the increase is damped (Fig. 3).

The term CTOR describes the changes in brain tissue oxygen that occur with changes in arterial oxygenation during hyperoxia. Various ethical and methodological problems mean that measurement of a normal CTOR is much more difficult than measurement of a normal COVR (Table 3).

Quantification

Van Santbrink and colleagues described the formula that is the most widely used for measuring CTOR:⁸²

$$CTOR = \% \Delta Pb_{O_2} / \Delta Pa_{O_2} \text{ (mm Hg)}$$

One of the problems with the van Santbrink method is that, for the same change in Pa_{O_2} , a small, and probably clinically insignificant, increase in Pb_{O_2} from 0.1 to 0.2 kPa (0.8 to 1.6 mm Hg) would give the same CTOR as an increase in Pb_{O_2} from 5 to 10 kPa (38 to 76 mm Hg).

Brain tissue oxygen normally has a linear relationship to Pa_{O_2} .^{59, 82} This relationship provides an alternative method of determining CTOR, which avoids the problems inherent in the van Santbrink method, CTOR being quantified by the gradient of the linear regression line. It is also essential to make measurements during periods of stable physiology. We have seen that that the process of equilibration between arterial and brain oxygen may be extremely prolonged (Fig. 4), which is probably a result of low perfusion. Therefore, in order to determine an accurate CTOR, sufficient time must be given for Pb_{O_2} to reach a steady state.

Depending on the increase in Pa_{O_2} and the degree of CTOR, both methods may rely on accurate measurements of a high Pb_{O_2} . This in itself may present a problem, as the sensors that are available are only designed to measure tissue oxygen accurately within a normal physiological range. What both methods lack is the ability to describe the clinical significance of the improvement in Pb_{O_2} . Various retrospective studies have shown that periods of low brain tissue oxygen correlate with an unfavourable neurological outcome after severe traumatic brain injury.^{5, 16, 17, 47, 59, 79–82, 85}

These data are consistent with studies showing that jugular venous desaturations correlate with poor neurological outcome,^{22, 65} however, one large study of 119 patients failed to show a significant correlation between either Pb_{O_2} or Sj_{O_2} and outcome.⁶⁹ The threshold for unfavourable outcome has been variably reported at between 0.8 and

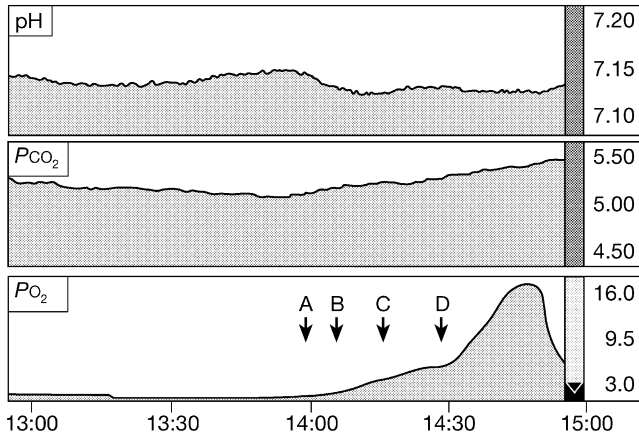


Fig 4 Neurotrend printout showing pH, carbon dioxide and brain tissue oxygen in response to changes in inspired oxygen ($F_{I_{O_2}}$) in a head-injured patient. A, $F_{I_{O_2}}$ 0.25 (start of monitoring); B, $F_{I_{O_2}}$ 0.5; C, $F_{I_{O_2}}$ 0.73; D, $F_{I_{O_2}}$ 0.98. All other physiological variables were stable during the study.

2.6 kPa (6–20 mm Hg). It is not known if prospective interventions aimed at achieving brain tissue oxygen levels above these thresholds affect outcome, but it would be useful if the calculation of CTOR indicated how changes in Pb_{O_2} related to these potentially beneficial thresholds.

Normal values

Using van Santbrink's formula, Menzel and colleagues⁵⁷ described a normal CTOR, measured in the frontal lobe of healthy anaesthetized piglets, as 0.21 (SD 0.12). CTOR has been assessed in humans, in non-pathological brain tissue of patients undergoing neurosurgery for brain tumours.²¹ Changes in Pa_{O_2} may not only affect Pb_{O_2} but also its homogeneity in tissues. Eintrei and Lund²¹ used a multiwire electrode to measure cortical tissue oxygen and showed that, once the inspired oxygen reached 30%, brain tissue oxygen became more scattered, heterogeneity increasing as the inspired oxygen increased to 100%. Only three of the six patients studied had an increase in mean brain tissue oxygen when on oxygen 100% compared with normoxia. The same group also studied the effects of hyperoxia on pig cerebral cortex,²¹ where a similar increase in tissue oxygen heterogeneity was seen. All six pigs showed an increase in mean tissue oxygen with hyperoxia but the reactivity varied widely. Regional CBF was estimated in the pigs using a washout curve of locally applied ^{133}Xe . Although, when compared with levels at an inspired oxygen fraction of 0.21, CBF fell by an average of 40% at an inspired oxygen fraction of 1.0, the extent of the reduction in CBF did not correlate with the changes in brain tissue oxygen.

Pathological values

Four studies have investigated oxygen reactivity in humans with cerebral pathology (Table 4).^{48 55 59 82} Both van Santbrink and colleagues⁸² and Menzel and colleagues⁵⁹ found a significant correlation between high oxygen reactivity and poor outcome (Glasgow Outcome Score 1,

2 or 3) after traumatic brain injury, the differences in reactivity being most significant on day 1. Neither study was powered to find a difference; this was an incidental statistical finding. Van Santbrink and colleagues⁸² also found that patients who had high brain oxygen levels had significantly higher oxygen reactivity, perhaps representing deranged oxygen reactivity during the hyperaemic stage after a head injury. The same group also looked at the response of Pb_{O_2} to induced changes in Pa_{CO_2} , and found that the response on day 1 was significantly lower than on days 3 and 5 after traumatic brain injury, a result also found by Carmona Suazo and colleagues.⁸ Impairments in brain oxygen 'carbon dioxide reactivity' are further evidence of impaired vascular reactivity after traumatic brain injury, which did not correlate with outcome. Meixensberger and colleagues⁵⁵ found higher CTORs in pathological brain tissue than in normal brain tissue, whereas Kiening and colleagues⁴⁸ found a lower CTOR close to lesioned areas.

Other factors that have been shown to influence CTOR include hypercarbia and depth of isoflurane anaesthesia, both of which increase CTOR.^{33 34} It appears that non-physiological vasodilatation (i.e. true hyperaemia) results in an increase in CTOR.

Clinical significance

Pathophysiological implications. A high CTOR could represent one of two possible scenarios. It could either represent vasomotor paralysis or it could be an appropriate physiological response to ischaemia. Even normal or high Pb_{O_2} values do not exclude tissue hypoxia. Mitochondrial dysfunction is being increasingly recognized after severe traumatic brain injury, and this could certainly result in high tissue oxygen levels despite histotoxic hypoxia.⁸³

Prognostic inferences. As mentioned previously, a significant relationship between CTOR and outcome after traumatic brain injury has been found in two studies.^{59 82}

Therapeutic interventions. Only one study has assessed the impact of hyperoxia on cerebral ischaemia after severe TBI.⁵⁸ It was found that increasing inspired oxygen from 35% to 100% for 6 h led to a 359 (SD 39)% increase in brain tissue oxygen and a 40% decrease in brain lactate concentration. The lactate/pyruvate ratio, which is more commonly used as an indicator of the redox state of the brain,⁴¹ was not assessed.

It is certainly possible to increase brain tissue oxygen levels from an ischaemic level to a non-ischaemic level by increasing the inspired fraction of oxygen, but there are no randomized controlled trials assessing the impact of brain tissue oxygen-targeted therapy after traumatic brain injury. The effects of hyperoxia on cerebral metabolism and ischaemia require further exploration using techniques such as microdialysis, phosphorus and proton magnetic resonance spectroscopy, and magnetic resonance diffusion-weighted imaging.

Table 4 CTOR studies

Study	Probe	Position	Patient numbers	Time	Method	Results	Comments
Meixensberger <i>et al.</i> , 1993 ⁵⁵	Modified Clark	Cortical surface, avoiding pial vessels	26 patients undergoing elective craniotomy. Divided into 2 groups, normal and pathological, depending on CT/MRI appearances of cortex. Pathological further separated depending on the degree of oedema on CT/MRI and presence of swelling after opening dura	At time of surgery	Increase inspired oxygen to 100%	Significant difference, between normal and pathological groups, in % brain oxygen change (137.8 vs 352, $P=0.0095$)	Relative oxygen reactivity not calculated. Significant differences in arterial oxygen and brain temperature between normal and pathological groups at baseline
van Santbrink <i>et al.</i> , 1996 ⁸²	Licox	Right frontal	18 with traumatic brain injury	Daily for 5 days	Correlation between arterial and brain oxygen Increase inspired oxygen to 100% in steps. CTOR calculated	Significant correlation between arterial and brain oxygen concentration in pathological group (correlation even stronger in oedema subgroup) at baseline F_{I_2} , and 100% oxygen Mean CTOR 0.7. Significant difference in mean and day 1 CTOR between favourable [0.55 (SD 0.41)] and unfavourable [0.94 (0.48)] 6 month outcome	Study was not powered to find a difference in outcome; this was an incidental statistical finding. Area of the brain monitored in relation to the site of injury was not specified. Not all of the 18 patients studied were studied every day (maximum number on any one day was 16)
Kiening <i>et al.</i> , 1998 ⁴⁸	Licox	Bifrontal, one probe close to lesion, one probe in normal tissue	6 TBI, 1 SAH	Days 2–12 after insult	16 oxygen reactivity tests, 1–3 per patient. Exact method not specified	Reduced oxygen reactivity in lesioned area	Oxygen reactivity not quantified. Reactivity only different when there were differences in brain tissue oxygen between the two probes
Menzel <i>et al.</i> , 1999 ⁵⁹	Paratrend	Right frontal, non-injured region	14 with traumatic brain injury	Within 14 h of admission to intensive care unit	Increase inspired oxygen to 100% in steps. CTOR calculated	CTOR range 0.2–2.1, mean 0.7. Significant difference in CTOR between favourable (GOS 1, 2, 3), 0.4 ± 0.2 , and unfavourable (GOS 4,5), 0.9 ± 0.6 , 3 month outcome	Area of the brain monitored in relation to site of injury was not specified. Study was not powered to find a difference in outcome; this was an incidental statistical finding.

SAH=subarachnoid haemorrhage, TBI=traumatic brain injury. For other abbreviations see footnote to Table 1. For method of calculation of CTOR see text.

Mechanisms

The mechanisms that lie behind hyperoxia-induced changes in tissue blood flow and the regulation of tissue oxygen partial pressures remain unclear. In human skeletal muscle, hyperoxia causes an increase in the mean tissue oxygen partial pressure, but with significant heterogeneities, with some regions of the tissue actually showing reduced oxygen pressures compared with normoxia.⁵¹ This increase in tissue oxygen heterogeneity with hyperoxia is also seen in the brain in both pigs^{21 72} and man.²¹ The increase in heterogeneity is speculated to be a result of redistribution of blood flow, with vasoconstriction in some areas and shunting in others. Various mediators and mechanisms have been suggested to play a role in COVR, including increased effects of serotonin,^{75 76} nitric oxide synthase inhibition,⁷¹ inhibition of endothelial prostaglandin synthesis⁶⁰ and increased leukotriene production.^{39 40}

Despite a number of advances in the last decade, the exact site and mechanism of the oxygen sensor is yet to be fully elucidated and, indeed, there may be more than one sensor.³⁸ Many physiologically relevant genes are activated during conditions of hypoxia, including those encoding erythropoietin, vascular endothelial growth factor, inducible nitric oxide synthase and glycolytic enzymes. Remarkably, at the transcriptional level, these diverse genes are all under the control of a crucial transcription factor: hypoxia-inducible factor 1 (HIF-1).²⁴ HIF-1 is a heterodimeric protein complex composed of two subunits: a constitutively expressed β -subunit and an α -subunit, the expression and activity of which are controlled by the intracellular oxygen concentration. During normoxia, HIF-1 α is rapidly degraded by the ubiquitin proteasome system, whereas exposure to hypoxic conditions prevents its degradation.^{35 36} This oxygen-dependent instability may provide a means by which gene expression is controlled during changes in oxygen tension (Fig. 5). We speculate that hyperoxia reduces the intracellular HIF-1 concentration, thus reducing the activity of important enzymes involved in glycolysis, such as phosphofructokinase and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase. A reduction in glycolysis would reduce lactic acid production and intracellular buffering, and thus modulate CBF. Indeed, we have seen that, in healthy volunteers, hyperoxia modulates the haemodynamic response to hyperventilation, and we speculate that this is a result of reduced HIF-1 concentration and a decrease in lactic acid production and intracellular buffering.⁴² The effects of hyperoxia on cerebral glycolysis, metabolism and ischaemia could be further explored using techniques such as microdialysis, phosphorus or proton magnetic resonance spectroscopy, and magnetic resonance diffusion-weighted imaging. However, it is unlikely that it will be possible to measure HIF-1 concentrations *in vivo* because of its intracellular position, large size and instability. It should certainly be possible to explore the effects of hyperoxia on HIF-1 in the laboratory using cultured cell lines.

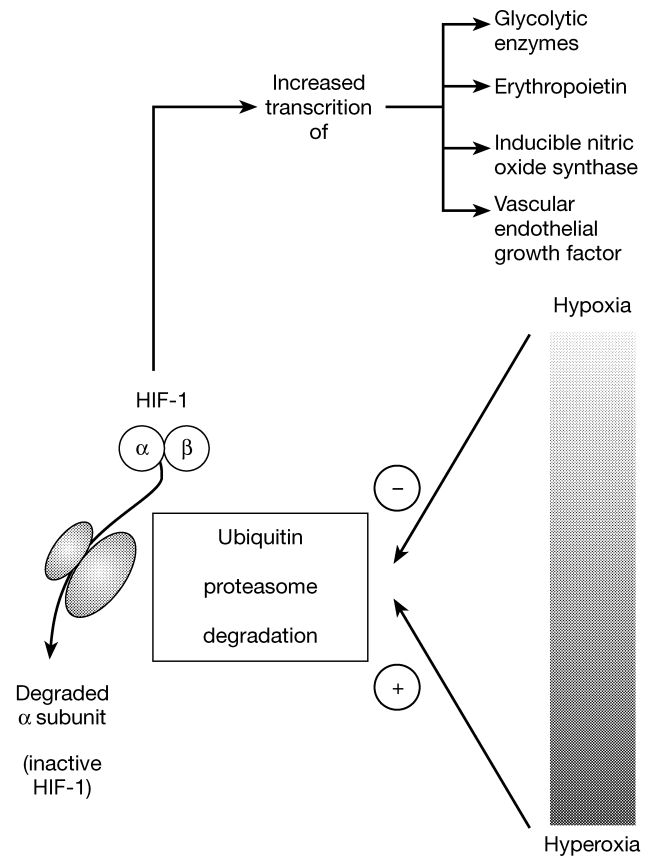


Fig 5 Many physiologically relevant genes are activated during conditions of hypoxia, including those encoding erythropoietin, vascular endothelial growth factor, inducible nitric oxide synthase and glycolytic enzymes. At the transcriptional level these diverse genes are all under the control of a crucial transcription factor: hypoxia-inducible factor 1 (HIF-1). HIF-1 is a heterodimeric protein complex composed of an α and β subunit. During normoxia, HIF-1 α is rapidly degraded by the ubiquitin proteasome system, whereas exposure to hypoxic conditions prevents its degradation. This oxygen-dependent instability may provide a means by which gene expression is controlled during changes in oxygen tension.

Conclusions

There is substantial evidence that CBF falls during periods of hyperoxia, this fall having been variably reported between 10 and 27% in healthy volunteers. There is some evidence that COVR is disturbed by vascular disease and traumatic brain injury.

Normal CTOR has not been well defined but it seems to be influenced by carbon dioxide, isoflurane anaesthesia and cerebral pathology, including traumatic brain injury. Although CTOR has been shown in two studies to have prognostic significance after traumatic brain injury, further work needs to be done in this field. Temporal and spatial profiles of brain tissue oxygen reactivity need to be better defined, as do the influences of anaesthesia and sedation, temperature and vasoactive agents. We have seen that brain tissue oxygen does not always have a linear relationship with arterial oxygen, and that the process of equilibration

between arterial and brain oxygen may be extremely prolonged (Fig. 4). For these reasons, definitions for CTOR need to be more tightly defined.

If COVR and CTOR are to be used for diagnostic or prognostic purposes, or to direct therapy, then the methodological issues surrounding their measurement must be taken into account and future studies must be based on a firm methodological foundation.

Whether poor COVR and supranormal CTOR describe the same phenomenon is not yet known. How COVR and CTOR integrate with more classic autoregulatory mechanisms requires investigation, as do the basic physiological mechanisms that lie behind COVR and CTOR. Abnormal pressure autoregulation and carbon dioxide reactivity are known to correlate with poor outcome after traumatic brain injury;^{12 53 63 70 73} further work is required to assess whether COVR and CTOR offer complementary information. Positron emission tomography, and magnetic resonance imaging using hyperpolarized gases or perfluorocarbons, may allow further exploration of the relationships between brain tissue oxygen, CBF, end-capillary oxygen tension, COVR and CTOR.^{18 20 27}

Further studies are required to determine whether hyperoxia can provide clinical benefits in patients with brain injury. At an appropriate stage, such studies should include a randomized controlled trial assessing the use of high fractions of inspired oxygen in the management of severe traumatic brain injury.

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