The role of tissue oxygen monitoring in patients with acute brain injury

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Cerebral ischaemia is implicated in poor outcome after brain injury, and is a very common post-mortem finding. The inability of the brain to store metabolic substrates, in the face of high oxygen and glucose requirements, makes it very susceptible to ischaemic damage. The clinical challenge, however, remains the reliable antemortem detection and treatment of ischaemic episodes in the intensive care unit. Outcomes have improved in the traumatic brain injury setting after the introduction of progressive protocol-driven therapy, based, primarily, on the monitoring and control of intracranial pressure, and the maintenance of an adequate cerebral perfusion pressure through manipulation of the mean arterial pressure. With the increasing use of multi-modal monitoring, the complex pathophysiology of the injured brain is slowly being unravelled, emphasizing the heterogeneity of the condition, and the requirement for individualization of therapy to prevent secondary adverse hypoxic cerebral events. Brain tissue oxygen partial pressure ($P_{bO_2}$) monitoring is emerging as a clinically useful modality, and this review examines its role in the management of brain injury.

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Severe traumatic brain injury (TBI) has a mortality exceeding 40% in the UK; ischaemia playing a significant part.26 27 Neuronal excitotoxicity, oxidative stress, mitochondrial dysfunction, lipid peroxidation with loss of membrane integrity and disturbances in ion homeostasis, free radical production, subsequent inflammation, necrosis and even apoptosis all play a role in the cascade of post-ischaemic events.3 101 With targeted therapy having shown promising reductions in mortality,70 21 11 brain tissue oxygen monitoring may provide a further tool not only to elucidate the pathophysiology, but also individualise therapeutic targets.65

Cerebral oxygenation and cerebral perfusion pressure targets

Cerebral blood flow (CBF) is regulated by metabolic requirements under normal conditions, so-called flow-metabolism coupling, and ensures adequate cerebral oxygenation. Temporal patterns of CBF disturbances after traumatic brain injury (TBI) have been well documented,2 58 with optimal therapy on the first post-injury day, not necessarily the most appropriate on subsequent days. High intracranial pressures (ICPs) and cerebral hypoxia show strong correlations with poor outcome,47 making the control of these parameters with a sufficient cerebral perfusion pressure (CPP) critically important (see the review by Steiner and Andrews in this postgraduate issue). The exact level of CPP required following TBI has been subject to much debate,68 76 86 the latest definitive guidance being the downward revision of the Brain Trauma Foundation’s guidelines on CPP targets (available from http://www2.braintrauma.org/guidelines) in 2003, suggesting a CPP target of 60, rather than 70 mm Hg. The proviso is, however, that in selected patients, where there is evidence of regional or global ischaemia, the CPP target may need to be higher. Individualized CPP optimization, therefore, becomes dependent on, amongst other things, the monitored levels of brain oxygenation.

Existing monitors of cerebral oxygenation

Imaging

Positron emission tomography (PET)

Metabolic imaging of the brain after $^{15}$O-radioisotope administration, allows the quantification of CBF, cerebral blood volume, the oxygen extraction fraction (OEF) and cerebral metabolic rate for oxygen (CMRO$_2$). Despite limitations, including the ‘snapshot’ nature of the technique, limited availability, use of radiation, poor spatial resolution and
the fact that the most unstable patients may not get scanned (selection bias), PET is still regarded as the ‘gold standard’ for visualizing cerebral oxygen use. Early post-injury PET has identified the presence of regional ischaemia, with quantification of the ischaemic brain volume.

**Magnetic resonance spectroscopy (MRS)**

MRS is an application of magnetic resonance imaging (MRI) whereby spectra of metabolic changes in living tissue are obtained. The outcome predictive value of non-invasively measuring brain metabolites (biomarkers of injury processes) using MRS, is increasingly being demonstrated. Measurement of adenosine triphosphate (ATP) using phosphorous spectroscopy (31P-MRS) and lactate using proton spectroscopy (1H-MRS) after brain injury can provide evidence of cerebral ischaemia, while N-acetyl aspartate represents neuronal integrity. The post-processing and availability of MRS preclude its routine clinical use at present.

**Bedside**

**Jugular venous oximetry (SjO2)**

Catheterization of the internal jugular vein to measure the oxygen saturation of the effluent cerebral blood at the jugular bulb, allows assessment of the global oxygenation status of the brain, providing some insight into the adequacy of CBF, especially during manoeuvres such as hyperventilation. A significant association between jugular venous desaturation and poor neurological outcome exists, with poor outcome in 55% of patients with no episodes of desaturation, 74% with one episode and 90% with multiple episodes. A shortcoming, however, is the inability of SjO2 to detect regional ischaemia, with PET evidence of approximately 13% of the brain being ischaemic before SjO2 levels decrease below 50%.

**Near-infrared spectroscopy (NIRS)**

Penetration of human tissue by light in the near-infrared band and its resultant absorption and scatter allows assessment of cerebral changes in oxyhaemoglobin (HbO2), deoxyhaemoglobin (Hb) and cytochrome oxidase. An attractive non-invasive regional monitor of cerebral oxygenation, NIRS has been beset by issues of extra-cranial blood contamination, light shielding, optimal optode placement, sample volume inaccuracies and the robustness of the derived algorithms. Spatial resolution and equipment improvements are addressing these issues, but to date NIRS has yet to find a clear role in routine clinical practice.

**Intracerebral microdialysis**

Microdialysis (the subject of a separate review by Smith and Tisdall in this postgraduate issue) has become a feasible clinical bedside technique in the intensive care unit (ICU), with metabolic patterns supplying valuable information on the adequacy of cerebral oxygenation.

**Brain tissue oxygen tension (PbO2)**

Improvements in technology, and the pitfalls of the techniques described above, have led to the introduction of brain tissue oxygen monitoring.

**What is brain tissue oxygen partial pressure?**

PbO2 is the partial pressure of oxygen in the extra-cellular fluid of the brain and reflects the availability of oxygen for oxidative energy (ATP) production. It represents the balance between oxygen delivery and consumption, and is influenced by changes in capillary perfusion. Distance from the supplying capillaries and possible barriers to oxygen diffusion may be particularly important after injury. An experimental global ischaemia model examining the relationships between PbO2, local CBF and NIRS-derived CMRO2 and AVDO2 (arterio-venous difference in oxygen content) has also suggested that the relative predominance of arterial or venous vessels in the immediate proximity of the PbO2 sensor may determine whether coupling exists between PbO2, CBF or PbO2 and OEF (AVDO2), respectively.

**The equipment**

The two most commonly used systems to date are the Licox (GMS, Kiel-Miellendorf, Germany) and the Neurotrend (Codman, Johnson & Johnson, Raynham, MA, USA). With good temporal resolution of acute biological changes, accomplished by the rapid response rates of the PbO2 systems, timely therapeutic interventions and assessment of the subsequent responses is possible.
Measurement principles

The Licox system provides $P_O_2$ measurement, with or without brain temperature (thermocouple), in an estimated 7.1–15 mm$^2$ $P_O_2$-sensitive area. The $P_O_2$ probe utilizes a closed polarographic (Clark-type) cell with reversible electrochemical electrodes (Fig. 1). Oxygen, which has diffused from the brain tissue across a semi-permeable membrane, is reduced by a gold polarographic cathode producing a flow of electrical current directly proportional to the oxygen concentration. This oxygen-consuming process is temperature-dependent.

In addition to $P_bO_2$, Neurotrend also offers $P_bCO_2$, pH and temperature. Its predecessor, the Paratrend 7, was an intra-arterial monitor which was adapted for intracerebral use. Although Neurotrend has been used both for research and clinical purposes, its manufacture has now been discontinued. The Neurotrend (Fig. 2) comprises three optical sensors ($P_bO_2$, $P_bCO_2$ and pH) and a thermocouple contained within the distal 25 mm of a 0.5 mm diameter microporous polyethylene tube. $P_O_2$ measurement occurs by quenching (reduction) of the intensity of a fluorescent optical emission from an indicator (ruthenium) in the presence of oxygen (following light pulses from a blue light emitting diode). In contrast to the Licox, this process does not consume oxygen and does not affect the measured oxygen level. The pH sensor relies on optical absorption, the local pH affecting the intensity of light transmitted through an indicator (phenol red). The $PCO_2$ sensor, similarly, is a CO$_2$-selective pH sensor.

Calibration and insertion

Using a sensor-specific pre-calibrated smart card, the Licox sensor can be inserted without delay, while the less user-friendly Neurotrend sensor requires a 31 min calibration in a chamber using three calibration gases before insertion. Sensors can be inserted, either via a cranial access device sited through a craniotomy, on the ICU, or under direct vision at surgery. Purpose-designed triple lumen cranial access devices allow simultaneous ICP, intracerebral microdialysis and $P_bO_2$ monitoring. Ideally, this should occur in an anatomically similar area of white matter where $P_bO_2$ readings are likely to be more stable. Post-insertion CT confirmation of probe position in the brain parenchyma (Fig. 3) is important for interpretation of readings. Transiently increasing the $FI_O_2$ and observing the corresponding $P_bO_2$ increase, is advised to exclude the presence of surrounding micro-haemorrhages or sensor damage at insertion. A 'run-in' or equilibration time of up to a half hour is required before readings are stable. Adjustment of insertion depth (when used through an access device) is allowed by the Neurotrend, but not the Licox.

Comparison

Comparative studies have been carried out to evaluate their functioning and reliability under experimental and clinical conditions. In test conditions, the Licox was slightly more accurate, with the Neurotrend under-reading at low $P_bO_2$. Both sensors displayed slight drift towards lower oxygen concentrations over time, but this was not thought to prohibit long-term use. The Neurotrend measured $P_bCO_2$ and pH very accurately. Clinically, the Neurotrend sensor under-read $P_bO_2$ (in contrast to the reported overestimation of the Paratrend 7), and was less robust than the Licox sensor.
Table 1  Studies relating brain tissue oxygen partial pressure measurements to monitored variables of cerebral oxygenation and blood flow. \(S_jO_2\), jugular venous oximetry; NIRS, near-infrared spectroscopy; rCBF, regional cerebral blood flow; CT, computed tomography; PET, positron emission tomography; TBI, traumatic brain injury; SAH, subarachnoid haemorrhage; TOI, tissue oxygenation index; L/P, lactate/pyruvate.

<table>
<thead>
<tr>
<th>Comparison modality</th>
<th>Authors</th>
<th>Study (pathology)</th>
<th>Year</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct local venous gas tensions</td>
<td>Edelman and colleagues(^{20})</td>
<td>Animal (normal)</td>
<td>2000</td>
<td>Local tissue and cerebral venous blood (PO_2) were highly correlated ((P&lt;0.001))</td>
</tr>
<tr>
<td>(S_jO_2)</td>
<td>Kiening and colleagues(^{43})</td>
<td>Human (TBI)</td>
<td>1996</td>
<td>Significant correlation between (S_jO_2) and (PO_2), (r^2=0.71)</td>
</tr>
<tr>
<td>(S_jO_2)</td>
<td>Gupta and colleagues(^{29})</td>
<td>Human (TBI)</td>
<td>1999</td>
<td>Significant correlation between (S_jO_2) and (PO_2) in areas without focal pathology ((r^2=0.69))</td>
</tr>
<tr>
<td>NIRS and (S_jO_2)</td>
<td>Gopinath and colleagues(^{28})</td>
<td>Human (TBI)</td>
<td>1999</td>
<td>Significant correlation between (S_jO_2) and (PO_2), (r^2=0.58)</td>
</tr>
<tr>
<td>rCBF using xenon CT</td>
<td>Doppenberg and colleagues(^{19})</td>
<td>Human (TBI)</td>
<td>2003</td>
<td>(PO_2) correlated with local CBF ((r=0.66), (P=0.02))</td>
</tr>
<tr>
<td>Local CBF using laser Doppler flow</td>
<td>Critchley and Bell(^{13})</td>
<td>Animal (SAH)</td>
<td>2003</td>
<td>(PO_2) correlated with rCBF ((r=0.36), (P&lt;0.01))</td>
</tr>
<tr>
<td>rCBF using thermal diffusion PET</td>
<td>Jaeger and colleagues(^{46})</td>
<td>Human (TBI and SAH)</td>
<td>2002</td>
<td>In normal areas: (\delta PO_2) during hyperventilation correlates with (\delta PO_2) (\text{calculated from OEF}) ((p=0.78), (P=0.0035))</td>
</tr>
<tr>
<td>Microdialysis</td>
<td>Zauner and colleagues(^{102})</td>
<td>Human (TBI)</td>
<td>1997</td>
<td>(PO_2) correlated with brain glucose ((P&lt;0.01)), but not lactate</td>
</tr>
<tr>
<td>Microdialysis</td>
<td>Meixensberger and colleagues(^{62})</td>
<td>Human (TBI and SAH)</td>
<td>2001</td>
<td>(PO_2), only weak negative correlation with L/P ratio (SAH: (r=-0.185), TBI: (r=-0.358))</td>
</tr>
<tr>
<td>Microdialysis</td>
<td>Sarrafzadeh and colleagues(^{79})</td>
<td>Human (TBI)</td>
<td>2003</td>
<td>(PO_2), 10–15 mm Hg for &gt;5 min: increased glutamate ((P=0.03)) (PO_2&lt;10) mm Hg for &gt;5 min: increased glutamate ((P=0.007)) and increased lactate ((P=0.044))</td>
</tr>
<tr>
<td>Microdialysis</td>
<td>Hlatky and colleagues(^{54})</td>
<td>Human (TBI)</td>
<td>2004</td>
<td>(PO_2&lt;10) mm Hg: increased lactate ((P=0.015))</td>
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</table>

Validation with existing techniques

Establishing the relevance of a monitor requires validation of the measured variables and their relationships with the existing clinical and experimental techniques (Table 1).

Clinical utility

Normal values

Normal brain gas tension measurements have been acquired experimentally, but human measurements have been restricted to ‘normal’ values during neurosurgery and in ‘normal-appearing’ brain after TBI. A feline study\(^{100}\) revealed a normal \(PO_2\) of 42 (9) mm Hg [\(PCO_2\) of 59 (14) mm Hg, brain pH of 7.0 (0.2)], while a murine study\(^{15}\) measured a normal \(PO_2\) of 29.4 (12.8) mm Hg. Human recordings have varied from a \(PO_2\) of 37 (12) mm Hg [\(PCO_2\) of 49 (5) mm Hg, brain pH of 7.16 (0.08)]\(^{36}\) to a \(PO_2\) value of 48 mm Hg\(^{60}\) in uncompromised patients undergoing cerebrovascular surgery.

Hypoxic thresholds

The identification of hypoxic tissue allows the institution of early potentially corrective interventions, and also provides meaningful therapeutic end-points. These values need to be considered in the context of probe type, probe site, underlying pathology and duration of hypoxia before irreversible damage occurs. Various \(PO_2\) hypoxic thresholds (Table 2) have been proposed.

Safety

Initial concerns regarding the invasiveness of these parenchymal sensors and the risk of haemorrhage and infection, have proved unfounded. Eleven studies\(^{6\;9\;17\;62\;79\;91\;96-98\;102\;103}\) including 552 patients reported no infections and three iatrogenic haematomas with only one requiring surgical evacuation. Measurement accuracy with negligible zero drift was also a consistent finding.\(^{5\;17\;97\;98}\)

Drawbacks

Some of the reported problems include insertion trauma with subsequent gliosis and the ability to adequately position and secure sensors in position. The focal nature of these monitors must also be emphasized.

Global assumptions of a focal monitor

Jugular venous oxygen saturation (\(S_jO_2\)) monitoring provides global cerebral oxygenation determination and can be used to calculate the arterio-venous oxygen content difference. \(PO_2\) sensors are extremely localized, only sampling approximately 15 mm\(^2\) of tissue around the tip. The positioning of the sensor, however, becomes a vital question in the interpretation of the readings. In ‘tissue at risk’ regions near focal pathology, global assumptions cannot be made and the monitor is purely focal, but when positioned in areas of seemingly normal tissue, or in areas of diffuse injury, the \(PO_2\) can be regarded as an
Table 2  Human studies proposing hypoxic brain tissue oxygen thresholds. CT, computed tomography; $P_{vO_2}$, cerebral venous/end-capillary $P_{O_2}$; PET, positron emission tomography; OEF, oxygen extraction fraction

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Authors</th>
<th>Year</th>
<th>Proposed threshold [mm Hg (kPa)]</th>
<th>How the threshold was determined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paratrend 7</td>
<td>Zauner and colleagues$^{102}$</td>
<td>1997, 1998</td>
<td>25 (3.3)</td>
<td>$P_{O_2}$ of 26 mm Hg ≈ CBF (xenon CT) &lt; 18 ml per 100 g per min; all patients with $P_{O_2}$ &lt;25 mm Hg had a poor outcome Combined above data with a feline MCA occlusion study and outcome</td>
</tr>
<tr>
<td>Paratrend 7</td>
<td>Doppenberg and colleagues$^{19}$</td>
<td>1998</td>
<td>Between 19 and 23 (2.5 and 3) 10 (1.3)</td>
<td>Significantly greater diffusion gradients for oxygen ($P_{O_2}$) if $P_{O_2}$ &lt;10 mm Hg</td>
</tr>
<tr>
<td>Neurotrend</td>
<td>Menon and colleagues$^{46}$</td>
<td>2004</td>
<td>&lt;14 (1.9)</td>
<td>Significant linear relationship between $P_{O_2}$ and PET OEF ($r^2=0.21$, $P&lt;0.05$); mean normal OEF=40% associated with $P_{O_2}=14$ mm Hg</td>
</tr>
<tr>
<td>Neurotrend</td>
<td>Johnston and colleagues$^{50}$</td>
<td>2005</td>
<td>&lt;15 (2) for 4 h</td>
<td>Regression analysis: $S_{jO_2}$ threshold of 50% correlated with $P_{O_2}$ of 8.5 mm Hg</td>
</tr>
<tr>
<td>Licox</td>
<td>Kiening and colleagues$^{53}$</td>
<td>1996</td>
<td>8.5 (1.1)</td>
<td>Significant difference in 6 month outcome at threshold ≤5 mm Hg ($P=0.04$), suggested maintenance of $P_{O_2}$ between 10 and 15 mm Hg</td>
</tr>
<tr>
<td>Licox</td>
<td>van Santbrink and colleagues$^{46}$</td>
<td>1996</td>
<td>Between 10 and 15 (1.3 and 2)</td>
<td>Tobit regression analysis relating the time below thresholds of $P_{O_2}$ with likelihood of death. Much greater likelihood of death, the longer the $P_{O_2}$ &lt;20 mm Hg or any time of $P_{O_2}$ &lt;6 mm Hg</td>
</tr>
<tr>
<td>Licox</td>
<td>Valadka and colleagues$^{46}$</td>
<td>1998</td>
<td>20 (2.7) [6 (0.8)]</td>
<td>The relative risk of death was graded. Hypoxic thresholds are expressed as the depth and duration of hypoxia imparting a 50% risk of death</td>
</tr>
<tr>
<td>Licox</td>
<td>van den Brink and colleagues$^{47}$</td>
<td>2000</td>
<td>&lt;5 (0.6) for 30 min</td>
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<td></td>
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<td>&lt;10 (1.3) for 1 h 45 min</td>
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<td></td>
<td></td>
<td></td>
<td>&lt;15 (2) for 4 h</td>
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</tbody>
</table>

indicator of global oxygenation,$^{25, 29, 53, 97}$ allowing the use of $P_{O_2}$ as an endpoint in the optimization of CPP. Kiening and colleagues$^{53}$ compared the use of $S_{jO_2}$ and $P_{O_2}$ in normal frontal brain white matter, in 15 patients with severe TBI showing a strong correlation ($r^2=0.71$). Continuous $P_{O_2}$ could reliably be monitored twice as long as $S_{jO_2}$, with good quality data acquisition 95% of the time with $P_{O_2}$, as opposed to the 43% for $S_{jO_2}$. The requirement for repeated calibrations of the $S_{jO_2}$ measurement system contrasted starkly with the lack of post-insertion calibration requirement of the $P_{O_2}$ technique.

Dynamic indices

In addition to static baseline $P_{O_2}$ readings, oxygen regulatory mechanisms challenged dynamically, may provide insight into the underlying pathophysiology and outcome prediction.

$P_{O_2}$ reactivity

The increase in $P_{O_2}$ relative to an increase in arterial $P_{O_2}$ is termed brain tissue oxygen reactivity. It is believed that this reactivity is controlled by an oxygen regulatory mechanism (cf. CBF autoregulation), and that this mechanism may be disturbed after brain injury. van Santbrink and colleagues$^{46}$ examined the ‘brain tissue oxygen response’ (the degree of change in $P_{O_2}$ in response to changes in $P_{aO_2}$) and showed that greater responsiveness in the first 24 h post-injury was associated with an unfavourable outcome ($P=0.02$); with multiple logistic regression analysis supporting its value as an independent predictor of unfavourable outcome (odds ratio 4.8). The effect of $P_{aCO_2}$ on this mechanism was illustrated experimentally by Hoffman and colleagues$^{42}$ in dogs where $P_{O_2}$ reactivity was attenuated during hypo-capnoea, and emphasizing that when assessing $P_{O_2}$ reactivity, effects of $P_{aCO_2}$ need to be considered. To understand the normal relationships of $P_{O_2}$, with mean arterial pressure (MAP), and with changing $CO_2$ concentrations in the uninjured brain, Hempell and colleagues$^{32}$ studied 12 anaesthetized pigs. $P_{O_2}$ displayed a linear relationship with $CO_2$ ($r^2=0.70$) and a sigmoid curve with MAP between 60 and 150 mm Hg ($r^2=0.72$), and a linear correlation with CBF (measured using thermal diffusion probes) during $CO_2$ reactivity testing ($r^2=0.84$). The conclusion was that $P_{O_2}$ is strongly influenced by factors regulating CBF, namely $CO_2$ and MAP.

‘$P_{O_2}$ autoregulation’

Soehle and colleagues$^{84}$ introduced the concept of ‘$P_{O_2}$ autoregulation’, defined as the ability of the brain to maintain $P_{O_2}$, despite changes in CPP, thereby identifying appropriate individual CPP targets. Lang and colleagues$^{54}$ showed a significant correlation ($r=-0.61$) between static cerebral autoregulation (determined using CBF velocity in relation to changing CPP) and cerebral tissue oxygen reactivity (the rate of change of $P_{O_2}$ in relation to changing CPP) suggesting a close link between regulation of CBF and oxygenation.

Following these findings, manipulation of $P_{O_2}$ by altering $P_{aO_2}$ (by $F_{O_2}$ increases) or altering the CPP (by MAP increases, ICP decreases, or both) have been investigated with the view to therapy optimization and potential prognostication.
Applications of brain tissue oxygen monitoring

In humans, \( P_{bO_2} \) monitoring has predominantly been applied to the investigation and management of subarachnoid haemorrhage (SAH) (both on the ICU and during operation) and severe TBI (see above) on the ICU. Other applications have included, arterio-venous malformation (AVM) resection, tumour resection and for studying the effects of anaesthetic agents.

SAH and vasospasm on the ICU

Despite its invasiveness, the application of \( P_{bO_2} \) monitoring seems attractive for the continuous surveillance and detection of delayed vasospasm-induced ischaemia in patients with SAH in the ICU (in contrast to the traditional snapshot use of TCD). Kett-White and colleagues\(^5\) monitored 40 patients (35 after SAH and 5 after complex aneurysmal surgery) on the ICU with \( P_{bO_2} \) and intracerebral microdialysis, but only managed to show weak associations between episodes of low \( P_{bO_2} \), abnormal microdialysis and outcome. Possible reasons cited for the marked variability in measured \( P_{bO_2} \) readings were the variable distances from vasculature (oxygen gradients), grey/white matter influences (metabolic rates, varying depths attributable to gyri and sulci) and tissue heterogeneity. A study using Neurotrend in 10 SAH patients\(^7\) (three of whom developed vasospasm), showed a significant decrease in pH and increase in \( P_{bCO_2} \), (\( P<0.001 \)), but failed to show ischaemic \( P_{bO_2} \) levels. Meixensberger and colleagues\(^6\) prospectively studied 42 patients presenting with severe grade SAH and failed to demonstrate the value of \( P_{bO_2} \) as an early predictor of non-survival, citing reasons such as small patient numbers, accuracy of probe placement in the affected cerebral territory, efficacy of the implemented ‘triple H’ (hypervolaemia, hypertension, haemodilution) therapy, and the possibility that oxygen consumption may have been more depressed than CBF, resulting in unchanged \( P_{bO_2} \) values. The jury, therefore, remains out on the value of \( P_{bO_2} \) monitoring as an early warning of cerebral vasospasm in SAH patients on the ICU.

Aneurysm surgery

Intraoperative use of \( P_{bO_2} \) monitoring is both feasible\(^23\) and is a sensitive indicator of cerebral tissue at risk. Severe bleeds (Fisher grade 3) also significantly decrease \( P_{bO_2} \) (\( P<0.05 \)).\(^4\) Correctly positioned \( P_{bO_2} \) monitoring allows not only assessment of the effect and reversibility of temporary aneurysm clipping, but can also be indicative of the correct positioning of the subsequent permanent clip.\(^2\) Hypoxic \( P_{bO_2} \) levels confirmed compromised perfusion detected on preoperative single photon emission computed tomography (SPECT) and cerebral angiography.\(^3\) In a study of 46 patients undergoing craniotomy for aneurysm clipping,\(^5\) the majority of 31 patients who required temporary clipping of the parent vessel, showed decreases in \( P_{bO_2} \), with a level of \( P_{bO_2} \) < 8 mm Hg for 30 min being predictive of cerebral infarction. Another study\(^9\) found that \( P_{bO_2} \) monitoring during aneurysm clipping supplemented somatosensory evoked potential (SEP) monitoring in identifying ischaemia, especially in those patients where the baseline SEP was absent.

AVM surgery

\( P_{bO_2} \) measurement has been used to investigate the oxygenation of cerebral tissue supplied by vessels with AVMs.\(^3\) In total, 13 patients undergoing resection of AVMs were compared with 8 non-ischaemic patients undergoing aneurysmal surgery (the controls). Low \( P_{bO_2} \), but normal \( P_{bCO_2} \) and pH (in contrast with raised \( P_{bCO_2} \) and acidosis seen in acute occlusive disease with ischaemia\(^3\)) before AVM resection suggested low perfusion and chronic hypoxia with possible metabolic adaptation and subsequent hypometabolism, while the marked \( P_{bO_2} \) increases post-resection indicate hyperperfusion with its attendant problems. Apart from enhancing the understanding of AVM pathophysiology, this study reaffirms the feasibility of intraoperative \( P_{bO_2} \) monitoring.

Tumours

The extent and nature of the effects of oedema on brain tissue oxygen surrounding tumours was investigated perioperatively in 19 patients.\(^7\) MRI-based stereotaxis was used to guide sensor placement into the peritumoral area before craniotomy and the effects of dural opening and resection on the \( P_{bO_2} \) was noted. In patients with swelling, \( P_{bO_2} \) increased significantly on dural opening (\( P<0.05 \)), and post-resection (\( P<0.05 \)), implying the presence of ischaemic processes with oedema. This emphasizes the importance of maintaining adequate CPP in patients undergoing brain tumour surgery. \( P_{bO_2} \) monitoring during awake craniotomy for tumour resection has also been reported.\(^9\)

Anaesthetic drug pharmacodynamics

Studies investigating the dose effects of anaesthetic agents such as isoflurane,\(^4\) desflurane\(^3\) and propofol\(^1\) on cerebral autoregulation and oxygenation to levels of EEG burst-suppression have also utilized \( P_{bO_2} \) monitoring. The inhalational agents demonstrate a dose-related loss of autoregulation with corresponding increase in \( P_{bO_2} \) as long as the CPP is maintained, while propofol displays no such changes and flow-metabolism coupling remains intact.

Therapeutic and research interventions

The clinical utility and temporal responsiveness of \( P_{bO_2} \) to fraction of inspired oxygen (\( FIO_2 \)) increases, \( P_{ACO_2} \) changes (hyper- and hypoventilation) and haemorrhage to 70% blood loss or cardiac arrest with immediate subsequent resuscitation, were experimentally validated by Manley and colleagues.\(^5\) In addition, investigation of pathophysiological
mechanisms after brain injury in studies combining $P_{BO_2}$ monitoring with PET, have proposed the presence of microcirculatory abnormalities with significant gradients for oxygen diffusion in injured tissue. Structural evidence for these pathophysiological changes has also been well documented. As more data are accumulated regarding hypoxic thresholds, and the clinical and outcome significance of $P_{BO_2}$ in various clinical situations is established, the changes in baseline $P_{BO_2}$ levels in response to potential therapeutic or research interventions gives weight to their clinical value. Interventions include the following.

**Elevation of CPP**

A comparative study using dopamine or norepinephrine to elevate CPP from 65 to 85 mm Hg, showed no significant increase in the $P_{BO_2}$ values monitored in predominantly normal-appearing brain. However, targeted $P_{BO_2}$ sensors in CT hypodense lesions in nine patients (with hypoperfusion confirmed with SPECT) revealed significant improvements in $P_{BO_2}$ readings with induced hypertension ($r^2=0.74$). Significantly higher $P_{BO_2}$ has been shown at a CPP $\geq$70 mm Hg than $<70$ mm Hg in TBI patients ($P<0.001$)

![Fig 4 Bedside monitoring of a patient with severe TBI with the Neurotrend $P_{BO_2}$ sensor placed near a cerebral contusion. Increasing the cerebral perfusion pressure (CPP) from around 70 mm Hg to above 100 mm Hg reverses the cerebral hypoxia (ABP, mean arterial blood pressure; ICP, intracranial pressure; $P_{tO_2} = P_{BO_2}$; kPa, kilopascals).](image)

**Hyperventilation**

An experimental study in 12 healthy pigs comparing $P_{BO_2}$ (Licox), rCBF (thermal diffusion system) and metabolic microdialysis markers at baseline, during moderate ($P_{AO_2}=30$ mm Hg) and profound ($P_{AO_2}=20$ mm Hg) hyperventilation revealed that both moderate and profound
hyperventilation may cause insufficient regional oxygen supply and anaerobic metabolism. The value of \( P_{\text{bO}_2} \), as a monitor of excessive hyperventilation (cf. \( S_j_{\text{O}_2} \)) was illustrated in a head injury study of 90 patients\(^6\) where the \( P_{\text{aCO}_2} \) was decreased with hyperventilation and \( P_{\text{bO}_2} \) decreased significantly (\( P<0.001 \)). Importantly, the risk of secondary cerebral ischaemia with hyperventilation increased over time.

**Hypothermia**

Despite the negative findings of the National Acute Brain Injury Study: Hypothermia\(^1\) (no improvement in outcome using hypothermia to 33°C within 8 h of TBI) and the Intraoperative Hypothermia for Aneuerysm Surgery Trial\(^9^4\) (no improvement in neurological outcome using intraoperative hypothermia in good grade SAH), hypothermia is thought to reduce secondary brain injury following TBI by metabolic suppression and reduction of inflammation, free radicals, cytokines and excitatory amino acids. \( P_{\text{bO}_2} \) and direct brain temperature were measured in 58 patients after severe TBI\(^8^5\) and revealed decreases in the \( P_{\text{bO}_2} \) with mild hypothermia (34–36°C) accompanied by decreases in ICP and \( P_{\text{bCO}_2} \), and increases in brain pH. Decreased metabolic requirements and lowering of the \( P_{\text{bO}_2} \), critical threshold were concluded. Another \( P_{\text{bO}_2} \) study in 30 patients\(^2^8\) indicated that 35°C might be the optimal temperature after severe TBI.

**Decompressive craniectomy**

In patients with intractable intracranial hypertension, despite maximal medical therapy, surgical (either bi-frontal or unilateral) removal of a part of the skull may be considered. The theme of brain oxygen manipulation, and its effect on other cerebral tissue parameters have been well documented in a study by Clausen and colleagues\(^9\) where they demonstrated that \( P_{\text{bCO}_2} \) was significantly higher at 6 h post-injury in patients with poor outcomes compared with patients with good outcomes (\( P<0.05 \)). They also showed that \( P_{\text{bCO}_2} \) was significantly higher at a CPP below 70 mm Hg as opposed to higher (\( P<0.0001 \), and also significantly higher at a \( P_{\text{bO}_2} \) below 10 mm Hg as opposed to higher (\( P<0.0005 \)). These findings were in the face of a stable \( P_{\text{aCO}_2} \). Brain pH differences at these CPP and \( P_{\text{bO}_2} \) thresholds were also significant (both \( P<0.0001 \)). Low brain pH has also been correlated with adverse outcome (\( P=0.003 \)). These parameters may, therefore, also provide useful end-points in optimization of therapy. Brain temperature measurement (available with both Neurotrend and Licox) has allowed investigation of hyperthermia\(^7^8 9^0\) and hypothermia.\(^2^8 8^5 1^0^3\)

**Cerebral oxygenation and outcome prediction**

The theme of brain oxygen manipulation, and its effect on patient outcome, was first addressed in 1998 when Cruz\(^1^6\) demonstrated a significant improvement in 6 months outcome in a group of 178 patients who underwent jugular oximetry monitoring and manipulation of oxygen extraction, compared with a group of 175 patients receiving ICP/CPP-guided treatment alone (\( P<0.00005 \)). However,
Tissue oxygen monitoring in acute brain injury

Table 3 TBI studies demonstrating the value of brain tissue oxygen tension in outcome prediction (dichotomized outcome=alive vs dead/persistent vegetative state)

<table>
<thead>
<tr>
<th>Authors</th>
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<th>Sensor</th>
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The possible value of \( P_bO_2 \)-guided therapy may also have been demonstrated by a study\(^\text{80}\) comparing 36 patients with isolated severe head injuries to 44 patients with severe head injuries and severe extra-cranial injuries; both groups managed with ICP/CPP/\( P_bO_2 \) protocols and late surgical intervention for extra-cranial injuries. Revealing no significant difference in 6 month or 1 yr outcome, it contrasted with previous reports of increased mortality in head injured patients with significant co-existing extra-cranial injuries. Numerous severe head injury studies have correlated low \( P_bO_2 \) with adverse outcome (Table 3). There are no randomized controlled trials of \( P_bO_2 \)-guided therapy to date. Given the clinical feasibility and the increasing evidence of worsened outcome with low brain \( P_bO_2 \), prospective randomized \( P_bO_2 \)-directed studies are now essential.

The future

The invasiveness of the \( P_bO_2 \) technique will always be an issue and may limit its usefulness in patients with coagulopathy, for instance. Combining parameters such as ICP and \( P_bO_2 \) into a single probe may reduce the number of probes inserted, but the ideal remains a non-invasive monitor. Better integration of the collected data with continuous online derived indices at the bedside may also facilitate patient optimization. Routine use of dynamic challenges (e.g., increases in CPP or \( F_io_2 \) when cerebral hypoxia presents), may identify individualized therapeutic targets.

Conclusion

Brain tissue oxygen partial pressure measurement contributes to the prevention of delayed cerebral damage after TBI and SAH. The integrated, continuous monitoring of \( P_bO_2 \) is now accepted as being safe and feasible. Reliable bedside \( P_bO_2 \) monitoring, both at baseline, and during the course of interventions such as CPP manipulation and hyperventilation, complements the use of existing cerebral monitors, and with the increasingly multi-modal approach of cerebral monitoring and data recording, may allow appropriate individualization of therapy. The rapid response of \( P_bO_2 \) sensors to altering tissue oxygen levels, together with further \( P_bO_2 \) threshold data, will allow more accurate identification of adverse cerebral conditions. Coupled with modalities such as ICP, transcranial Doppler and brain chemistry (microdialysis), more timely intervention and prognostication may be allowed. \( P_bO_2 \) measurement, therefore, is emerging as a useful clinical tool and, taken within the context of
underlying pathology, probe positioning, and responses and trends, there is mounting evidence that $P_{bO_2}$-guided therapy may bring us a step closer to the goal of outcome improvement after brain injury.

Acknowledgement
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