Monitoring Cerebral Oxygenation: Recent advances

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INTRODUCTION

The goals of head injury management are limitation of disability and reduction of mortality. Although the primary damage that occurs at the time of the injury cannot be modified, secondary brain insults contribute to the extension of the area of injury. Many studies have also demonstrated that, after traumatic brain injury, the cerebral autoregulation is impaired and the injured brain is more susceptible to secondary insults. Therefore understanding the mechanisms of secondary brain insults is vital to the institution of appropriate therapy. A landmark study by Chesnut et al confirmed the importance of hypoxia and hypotension, the two most common causes of secondary insults, in determining outcome from neurotrauma.1 The final common pathway of secondary insult mediated brain damage appears to be through reductions in cerebral oxygen delivery. In support of this concept are data from other studies on cerebral blood flow and brain tissue oxygen measurements in patients with head injury.2, 3 Monitoring cerebral perfusion and oxygenation is therefore becoming commonplace in neurosurgical critical care practice.

The purpose of this review is to examine the physiology and pathophysiology of cerebral oxygenation, review the various modes of monitoring cerebral oxygenation, critically review the literature concerning their use in day to day intensive care practice, outline their limitations and define possible indications for their use.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF CEREBRAL OXYGENATION AND ISCHAEMIA

The brain has unique anatomical and physiological characteristics, which render it susceptible to ischaemia. The predominant substrates of cerebral energy metabolism are glucose and oxygen.1 The adult brain has a blood supply of 50 ml/100 g/min, an oxygen consumption of 45 ml/min and a CMRO₂ of 3.5 ml/100g tissue/min. Oxygen extraction by the brain is slightly greater than the whole body at rest as reflected by the
higher arterio-venous difference of 5-7 ml% as compared to 3-5 ml% for the whole body. There is differential vulnerability of the various parts of the brain to hypoxia. For example, the neurons are more vulnerable than the glial tissue, the cerebral cortex more than the brain stem and the grey matter more than the white matter. Furthermore, remote anatomical connections through axons and dendrites extend the injury from the primary focus. The closed cranial cavity and the absence of a lymphatic circulation increase the risk of infarction of the ischaemic penumbra and cerebral oedema under conditions of intracranial hypertension. The combination of small glucose reserves and high oxygen extraction limits the ability to sustain brain energy metabolism to about 20 seconds during total cessation of cerebral flow. Thus, even brief interruptions in cerebral blood flow produce disruption of cerebral auto-regulation and EEG and biochemical changes within the brain. The end result of ischaemia and cerebral hypoxaemia is lactic acidosis, ionic changes within the cell, excitotoxicity and free radical formation.

FACTORs DETERMINING CEREBRAL OXYGENATION

The three main factors determining cerebral oxygenation are cerebral blood flow (CBF), arterial oxygen content (CaO₂) and cerebral metabolic rate of oxygen consumption (CMRO₂). A variety of monitoring modalities are available and are listed in Table 1. They include:

1. Systems providing a global measurement of cerebral oxygenation;
2. Systems providing a regional measurement of cerebral oxygenation; and,

Table 1
Classification of cerebral oxygenation monitors

<table>
<thead>
<tr>
<th>A. Global cerebral oxygenation monitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Intracranial pressure (ICP) and cerebral perfusion pressure (CPP)</td>
</tr>
<tr>
<td>2. Measurement of cerebral blood flow (CBF)</td>
</tr>
<tr>
<td>3. Transcranial Doppler ultrasonography</td>
</tr>
<tr>
<td>4. Jugular venous oximetry</td>
</tr>
<tr>
<td>5. Cerebrospinal fluid gas tensions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Regional cerebral oxygenation monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Near infra red spectroscopy (NIRS)</td>
</tr>
<tr>
<td>2. Intraparenchymal probes</td>
</tr>
<tr>
<td>3. Laser Doppler flowmetry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Monitors of cerebral metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cerebral microdialysis</td>
</tr>
<tr>
<td>2. Cerebral bioenergetics</td>
</tr>
</tbody>
</table>

Global cerebral oxygenation monitors

_Intracranial pressure (ICP) and cerebral perfusion pressure (CPP)_

Cerebral blood flow is an important determinant of cerebral oxygen delivery. Its measurement with nitrous oxide or the Xenon 133 radiotracer is cumbersome and not practical in the ICU. The cerebral perfusion pressure is frequently used as an alternative for CBF measurements. CPP is calculated as the difference between the mean arterial pressure (MAP) minus the ICP. Reliable measurements of ICP are required to calculate CPP. To measure ICP reliably, a fluid filled intraventricular catheter or a solid state fiberoptic device is required. Fluid filled systems provide
accurate data, facilitate CSF drainage to decompress the ventricular system and are considered the “gold standard” to measure ICP. However, they have limited frequency response and present a risk of infection.¹⁰,¹¹ Solid state fiberoptic devices produce highly accurate data initially, are less invasive and easier to position, but do not allow CSF drainage and are more expensive.¹² The additional benefits of measuring ICP include the ability to analyze the arterial and ICP waveforms to evaluate the shift in amplitude and frequency and to determine intracranial compliance. Alterations in the ICP amplitude and pressure index have been shown to correlate with neurological outcome.¹³

With decreased intracranial compliance, small changes in intracranial volume can induce gross changes in ICP and therefore CPP. The relationship between intracranial pressure and volume is given by the pressure-volume index (PVI), which is defined as the change in intracranial volume that produces a ten-fold rise in ICP.¹⁴ The normal value is about 26 ml, but may be lower in patients with head injury. Thus, small reductions in intracranial volume may result in significant decrease in ICP. This may be achieved by mannitol or hypertonic saline which reduce cerebral swelling. Manoeuvres such as hyperventilation reduce cerebral blood volume, producing an acute reduction in intracranial volume and thus ICP.

The attraction of using CPP as an index of cerebral oxygenation is its linear relationship to CBF. Based on available data (which are predominantly Class II or Class III), an optimal CPP of 60-70 mmHg has been proposed in a number of studies with an increased likelihood of poor outcome if it is not maintained above this threshold.¹⁵

Caveats when interpreting ICP and CPP

The use of CPP as an index of CBF does not take into account the heterogeneity of CBF in head injury and the variability of cerebrovascular resistance. A “target CPP” may not guarantee adequate low CBF in the setting of vasospasm or other intracranial or carotid artery disease. Therapeutic measures designed to maintain an optimum CPP may by themselves induce cerebral ischaemia or produce serious systemic side-effects such as ARDS of high dose inotropes.¹⁶ The presence of patient dependent variations in the level of the optimum ICP should also be considered. ICP waveform analysis is a complex process and remains largely a research tool. Also, as CPP and CBF are haemodynamic variables, ideally they are interpreted in conjunction with arterio-venous differences for oxygen. The relationship between CBF and CMRO₂ is given by the cerebral extraction of oxygen. This forms the basis for jugular venous oximetry, which is discussed in detail below.

Transcranial Doppler (TCD)

TCD allows the measurement of blood flow velocity in the basal cerebral arteries using three naturally occurring acoustic windows — transtemporal, transorbital and transfenoral.¹⁷ The major cerebral arteries can be insonated using the transtemporal approach. The systolic, diastolic and the mean flow velocity are measured, while the pulsatility index is a derived variable, calculated as the difference between the systolic and the diastolic flow velocity divided by the mean flow velocity. A range of flow velocities has been described, depending on the artery and the age of the patient. A raised velocity, particularly in the setting of traumatic subarachnoid haemorrhage, may be indicative of vasospasm. Other useful information provided by TCD includes:
(1) cerebrovascular reactivity utilizing the response of flow velocity to changes in CO₂ concentration;
(2) spasm and hyperaemia, based upon the comparison between extracranial and intracranial flow velocity;
(3) an assessment of CPP using the pulsatility index; and,
(4) detection of brain death.18

The limitations of TCD include a variable relationship between velocity and flow,19 problems of long term fixation of the ultrasound probe, inter- and intra-observer variability in the measurement process,20 and marked moment to moment variability of velocity patterns in both volunteers and in patients. The latter may limit the usefulness of intermittent transcranial doppler.

**Jugular venous oximetry**

Jugular bulb oxyhaemoglobin saturation monitoring (SjO₂) has been widely purported to reliably assess the adequacy of the cerebral blood flow. The jugular venous saturation is directly proportional to CBF and arterial oxygen saturation (SaO₂) and inversely proportional to cerebral metabolic rate of oxygen (CMRO₂). It is measured using a catheter inserted into the dominant jugular bulb. The correct position of the catheter can be assessed by a lateral skull X-ray. The technique of insertion and calibration has been described by Andrews et al.21 SjO₂ can be monitored continuously by a fiberoptic catheter. If SaO₂ remains constant and CMRO₂ is assumed to be fixed, then changes in SjO₂ are proportional to changes in cerebral blood flow. Normal values range from 55-75%.

Despite the availability of data suggesting a relationship between jugular desaturations and poor outcome,22 there is no evidence to suggest that prevention and treatment of jugular venous desaturation improves outcome. Consequently, there has been a waning of enthusiasm for this mode of monitoring the last few years. Several other factors have also contributed to this loss of support. Investigations by Latronico et al. and Stocchetti et al. have demonstrated significant differences in measurement between the two sides,23, 24 thus raising the question of which side should be monitored. The invasive nature of the technique, the potential for erroneous readings resulting from catheter malposition, impaction and thrombus formation, and the likelihood of extracerebral contamination of jugular venous blood flow have also mitigated against its use.25-27 The SjO₂ data reflect global cerebral oxygenation and may miss important regional changes, as has been shown in comparison with brain tissue oxygen tension (PbO₂).28, 29 Changes in SjO₂ are an index of CBF only if CMRO₂ is assumed to be constant. This is not the case, however, in patients with neurotrauma, as they often have fever or seizures which will influence the CMRO₂.

**Measurement of cerebrospinal fluid (CSF) gas tensions and pH**

CSF is produced by the choroid plexus of the cerebral ventricles, circulates though the lateral, third and the fourth ventricles and enters the subarachnoid space through the Foramina of Luschka and Magendie. It circulates on the cortical surface of the brain in the subarachnoid space and is absorbed into the venous sinuses through the Pachionian granulations. Given its production in the “core” of the brain and its circulation through various compartments of the cranial cavity, it would seem logical that measurement of its gas tensions would reflect those of the brain. Venkatesh et al have demonstrated that aspiration of CSF and measurement of its gas tensions in a
blood gas analyzer produces inaccurate results.\textsuperscript{30} The only reliable way of measuring CSF gas tensions accurately is to use a continuous gas sensor. Venkatesh et al also demonstrated the feasibility of measuring CSF gas tensions continuously using such a gas sensor inserted through an intraventricular drain in patients with neurotrauma.\textsuperscript{31} However, they reported the potential for inaccurate results resulting from a clot or devitalized tissue present in the drain tip. The technique provides only a global index of brain oxygenation and necessitates the positioning of an external ventricular drain.

**Regional cerebral oxygenation monitors**

*Near infrared spectroscopy (NIRS)*

NIRS is a non-invasive technique developed for the continuous measurement of oxyhaemoglobin, reduced haemoglobin and cytochrome aa3 in brain tissue.\textsuperscript{32} It is based on the principle of absorption or transmission spectroscopy of infrared light. The attenuation of the incident beam of light can be attributed almost solely to absorption by oxyhaemoglobin, reduced haemoglobin and cytochrome aa3. The extent of light absorption is governed by the principles stated in the Beer & Lambert law.

Owing to the small size of the cranium and the thin vault, the technique has found more application in neonates than in adults.\textsuperscript{33} In adults, because of a longer path length of light, there is greater scattering of light, preventing adequate transmission to the opposite side of the skull.\textsuperscript{34} This necessitates sampling of scattered light by a probe placed ipsilateral to the source probe, resulting in a loss of resolution. The contribution of scalp blood volume to the overall absorption of light needs to be excluded from the final equation. The proportion of the various vascular compartments contributing to light absorption is only an estimate, based on previous studies and not an accurate measure.

Whilst studies have demonstrated the usefulness of NIRS in assessing the impact of respiration, changes in PCO\textsubscript{2} and carotid cross clamping on cerebral oxyhaemoglobin and reduced haemoglobin, its place in the monitoring of patients with head injury remains to be established.\textsuperscript{33,35} Studies comparing the sensitivity of NIRS with jugular venous oximetry to detect early cerebral hypoxia have produced conflicting results. NIRS requires further refinement and validation before recommending its routine use in clinical practice.

*Brain tissue pH, PCO\textsubscript{2} and PO\textsubscript{2} measurement*

The miniaturization of the Clark electrode and fiberoptic systems (optodes) has permitted the measurement of gas tensions and pH in tissues. These probes can be placed in the brain surgically either at the time of craniotomy or through a burr hole. For the first time, this technology has enabled us to measure tissue gas tensions in clinical practice. At the present time two systems are available for measurement of brain oxygen tension. Paratrend 7 sensor is a hybrid electrode-optode system and is capable of measuring pH, PCO\textsubscript{2}, PO\textsubscript{2} and temperature. It has been validated for use in bench studies, experimental animal models and in critically ill patients.\textsuperscript{31,36} The Licox sensor is a Clark electrode with a thermocouple to facilitate temperature compensation.\textsuperscript{37} The range for normal brain PO\textsubscript{2} has been reported to be 10-20 torr. In addition to measuring the absolute values of tissue gas tension, these systems also allow the derivation of “oxygen and carbon dioxide reactivity”, i.e. the change in tissue PO\textsubscript{2} and PCO\textsubscript{2} for a given change in arterial oxygenation or ventilation.\textsuperscript{38} This is used as a measure of cerebral autoregulatory status and a loss of reactivity correlates with
poor neurological outcome. A number of studies to date demonstrate that brain PO\textsubscript{2} measurement is a sensitive method of tracking cerebral oxygenation in neurotrauma.\textsuperscript{2} Furthermore, few adverse events related to these invasive probes have been reported.

There are a number of unanswered questions with these devices with regard to tissue oxygenation monitoring. Firstly, their insertion may be associated with tissue trauma. It has been previously demonstrated that the presence of clot and devitalized tissue may interfere with sensor measurements.\textsuperscript{31, 39} Secondly, in vivo calibration is not possible as the “true” tissue gas tension is not known. Thirdly, the scanning area for these sensors is variable, reported to be 20 mm\textsuperscript{2} for the Licox, which may not be large enough to detect ischaemia in the entire ischaemic penumbra. It has been shown that, on the cortical surface, brain PO\textsubscript{2} varies markedly over a distance of a few millimetres.\textsuperscript{40} The issues of infection risk and costs also need to be considered.

**Laser Doppler flowmetry (LDF)**

LDF provides a continuous measure of the surface blood flow over the cerebral cortex. The principle behind this technique is the conversion of the Doppler shift present in reflected light to provide an index of microcirculatory flux (the product of red cell concentration and red cell velocity). This method has been validated for measurement of regional cerebral blood flow.\textsuperscript{41} Besides real time measurement of cerebral microvascular blood flow, the influence of physiological and pharmacological stimuli on microcirculatory flow can be observed in detail. The limitations of the technique are the small area of tissue scanned, semiquantitative assessment of CBF, the need for surgical placement of cortical probes, the tendency for movement artifacts to influence signal quality and the limited experience with head injured patients.

**Monitors of cerebral metabolism**

**Cerebral Microdialysis**

This relatively new technique enables prolonged measurements of extracellular fluid metabolites in the brain tissue.\textsuperscript{42} One or more microdialysis catheters can be inserted through the same burr hole as an intraventricular catheter. The method uses an internally perfused semipermeable membrane probe, which allows water-soluble substances such as lactate, glucose, amino acids and electrolytes to be collected for analysis outside the brain. Normal saline is used as the perfusate. The results of the microdialysis can be influenced mainly by the length of the catheter and by the perfusion fluid and its rate. In combination with a measure of cerebral blood flow, the method provides a novel approach to studying the relationship between cerebral perfusion and metabolism.\textsuperscript{43} Fluctuations in concentrations of extracellular fluid metabolites may provide evidence of ischaemic damage (glucose, lactate, pyruvate, K, ADP) or excitotoxicity (glutamate, aspartate),\textsuperscript{44} or alteration in the phospholipids membrane caused by oxygen radicals.

The limitations of the microdialysis technique are its invasiveness, its ability to sample a small volume of cortical tissue and the potential for introduction of infection.\textsuperscript{45} Until data demonstrating an improvement in outcome using microdialysis generated endpoints become available, it can only considered a research tool.

**Monitoring cellular energetics**

With development in technology, emphasis is shifting from monitoring global parameters to measurement of substrate utilization at the level of the cell. The end
product of carbohydrate metabolism is the generation of ATP (38 molecules of ATP per molecule of glucose metabolized via the Krebs cycle). In the brain and muscle, a portion of this ATP is converted to creatine phosphate (CP). High-energy phosphate levels can be measured using freeze clamping, NIR spectroscopy and NMR spectroscopy.\textsuperscript{46, 47}

Freeze clamping involves invasive tissue sampling using a chilled instrument, rapid cooling and measurement of metabolites in the specimen. The technique is invasive, time consuming and does not lend itself to continuous measurement. NIR spectroscopy facilitates the measurement of tissue oxidized haemoglobin and cytochrome aa3. This technique has been described in detail in a previous section.\textsuperscript{P31} NMR spectroscopy allows the non-invasive measurement of high-energy phosphates within the cell.\textsuperscript{47} Refinement in this technology has permitted the measurement of brain metabolism in animals and humans.

Although they represent exciting developments in the area of cellular energetics, owing to their bulk, cost and potential electromagnetic interference with other ICU monitoring systems, the above techniques remain largely research tools with limited clinical application.

UNANSWERED ISSUES IN CEREBRAL OXYGENATION MONITORING

Despite a number of studies demonstrating potential usefulness of all the monitoring modalities discussed, there are still a number of unanswered questions with regard to the information generated. What is an appropriate level of brain PO\textsubscript{2} or SjO\textsubscript{2} to be maintained? Recently, data have emerged that apoptosis is a significant pathological process following neurotrauma and one which may have an impact on outcome. Critical PO\textsubscript{2} thresholds exist at which apoptosis may be triggered but these need to be identified in humans.\textsuperscript{48} If there is a decline in SjO\textsubscript{2} from 75% to 65%, is there a need to intervene even though this is a decrement within the normal range? What is the relationship between changes in SjO\textsubscript{2} and brain PO\textsubscript{2}? Is it the white matter or the gray matter or the gray white interface PO\textsubscript{2} that is most important? What is the safety record of the newer devices? For example, no single trial has been large enough to detect a complication rate of 1 in 1000. How long can tissue oxygen devices be left in place? One of the other problems is the lack of Class I data on the benefits of ICP monitoring, the appropriate ICP treatment threshold or the newer monitoring modalities. The above issues need to be clarified in large randomized controlled trials before drawing conclusions on usefulness, longevity of use and safety.

MONITORING CEREBRAL OXYGENATION — A REALISTIC OR AN ELUSIVE GOAL?

The ability to monitor cerebral oxygenation, either intermittently or continuously, is now possible. Some of the techniques, such as ICP, CPP, TCD and SjO\textsubscript{2} measurement are commonly used. Others are still primarily research tools. The complex and as yet incompletely understood physiology of the injured brain necessitates certain assumptions to be made when these devices are used. In order to overcome some of these limitations, there has been a shift towards multimodal monitoring to provide an increased power of interpretation. Clearly, some of the currently available techniques need further refinement and evaluation before justifying their routine use in clinical practice. The other requirements for the use of these systems are safety and that
management based on the information provided should lead to an improved patient outcome. The first step has certainly been made in that direction with the generation of more accurate data. With improved measurement and monitoring techniques, determination of critical tissue $PO_2$ thresholds for neurological recovery and thus titration of therapy to this level of tissue $PO_2$ becomes a possibility.

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