Neuromonitoring for Traumatic Brain Injury in Neurosurgical Intensive Care
Say Kiat Lee, MMed (Anaesthesiology), MBBS, June Pheck Suan Goh, FRCA (London), MBBS
Department of Anaesthesiology, Singapore General Hospital, Singapore

ABSTRACT
The primary aim of neuromonitoring in patients with traumatic brain injury is early detection of secondary brain insults so that timely interventions can be instituted to prevent or treat secondary brain injury. Intracranial pressure monitoring has been a stalwart in neuromonitoring and is still very much the main parameter to guide therapy in brain injured patients in many centres. Cerebral oxygenation is also established as an important parameter for monitoring: global cerebral oxygenation is reliably measured using jugular venous oxygen saturation while brain tissue oxygen tension measurement allows focal brain oxygenation to be monitored. Near-infrared spectroscopy allows a non-invasive option for monitoring of regional cerebral oxygenation. Cerebral microdialysis makes focal measurements of markers of cellular metabolism and cellular injury and death possible, and it is in transition from being a research tool to being an important clinical tool in neuromonitoring. Multimodal monitoring allows different parameters of brain physiology and function to be monitored and can improve identification and prediction of secondary cerebral insults. Multimodal monitoring can potentially improve outcomes in patients with traumatic brain injury by promoting customised treatment strategies for individual patients in place of the commonplace practice of strict adherence to achieving the same standard physiological targets for every patient.

Keywords: brain tissue oxygenation, cerebral microdialysis, intracranial pressure, jugular venous oxygen saturation, near-infrared spectroscopy

INTRODUCTION
There is little doubt that traumatic brain injury (TBI) is a major cause of mortality and disability throughout the world, especially among young people. It is well known that TBI sets off a series of events that can lead to secondary brain injury. These secondary insults consist of ischaemic, ionic, neurochemical and immunological processes, and can result in further damage to the injured brain. Causes of these secondary insults can be intracranial, such as intracranial hypertension, cerebral oedema, disturbances of regional cerebral blood flow, seizures, excitotoxicity, mitochondrial dysfunction and metabolic disturbances, or systemic, such as hypoxaemia, hypotension, glucose and metabolic derangements, and anaemia. The prevention and minimisation of such secondary injury to the brain has thus become the main therapeutic target of modern TBI management.

Neuromonitoring has become an essential tool for the intensive care physician for the timely identification and prevention of secondary cerebral insults. The primary objectives of neuromonitoring in TBI are to detect ongoing secondary brain injury, to guide therapy as well as to predict outcome. It is believed that if secondary insults can be recognised early, they can be better managed and outcome for patients can be improved. The Current Guidelines for the Management of Severe Head Injury stress the use of intracranial pressure (ICP) monitoring for the management of severe TBI patients. However, there has not been any randomised clinical trial to support its routine use. In contrast, multimodality monitoring has been advocated by some, although there is also no robust evidence to support that the use of such a monitoring method does improve the outcome of patients with severe TBI.
monitoring refers to the monitoring of several parameters of brain physiology and function, and comprises several invasive and non-invasive techniques, including monitoring of intracranial pressure, brain oxygenation, brain metabolism and neurochemistry, cerebral blood flow, and brain electrical activity and function. The vast array of information provided by multimodality monitoring may seem unwieldy to the uninitiated but to the experienced clinician, it is certainly advantageous to the management of severe TBI. Should one modality fail, one can always rely on the other modalities to provide information on brain physiology. This review is focused on the modalities of ICP monitoring, brain tissue oxygenation monitoring and neurochemical monitoring of severe TBI in the Neurologic Intensive Care.

INTRACRANIAL PRESSURE (ICP)

Despite the multitude of advances in neuromonitoring in recent years, ICP is still the most commonly monitored parameter in the neurosurgical intensive care unit. This is because the monitoring of ICP and its derived parameter, cerebral perfusion pressure (CPP), are important components of the management protocols for TBI in most units. There exists a vast quantity of clinical evidence to support the use of ICP monitoring in guiding therapeutic interventions and assessing prognosis, although there is a lack of Class 1 evidence to show the its benefit on outcome after severe TBI. Outcome prediction is improved with the addition of ICP monitoring, and it is established that a poor prognosis accompanies sustained elevation of ICP. A study of ICP of data from the Traumatic Coma Data Bank demonstrated that beyond the usual outcome predictors in age, admission motor score and abnormal pupillary responses, the proportion of time that ICP was above 20mmHg was highly significant in outcome prediction. The current guidelines by Brain Trauma Foundation (BTF) recommend ICP monitoring in all patients with severe head injury and either an abnormal computed tomographic (CT) head scan or a normal CT scan with at least 2 of the following risk factors: age >40 years; systolic blood pressure <90mmHg; unilateral or bilateral motor posturing. ICP monitoring allows the physician to institute therapeutic interventions to prevent or reduce ICP increases, and allows the physician to monitor the effectiveness of the therapy. The normal ICP is 7 to 15 mmHg in a supine adult. Therapy is indicated when ICP is >20mmHg in an adult with TBI.

However, 45 to 80% of patients with TBI develop intracranial hypertension with ICP >20mmHg despite treatment. Vik et al investigated the use of cumulative “dose” of intracranial hypertension by measuring the area under curve of ICP versus time in TBI patients and found a significant relationship between ICP “dose” and mortality rate, outcome and 6 months, and the worst Marshall CT classification.

The placement of a ventriculostomy catheter with the tip in a lateral ventricle, and the catheter connected to a standard pressure transducer, is considered the “gold standard” for ICP measurement. It measures global ICP, allows drainage of cerebrospinal fluid (CSF) to treat intracranial hypertension, allows in vivo calibration, and allows administration of drugs such as antibiotics. However, this is the most invasive of ICP monitoring methods and insertion of the ventricular catheter may be difficult if there is displacement of the ventricle due to severe cerebral swelling or the presence of an intracranial mass lesion. The rate of ventriculostomy-related infection is up to 11%. This method also does not allow simultaneous drainage of CSF and monitoring of ICP. As an alternative to ventricular catheters, probes with microtransducer tips can be placed in the brain parenchyma or the subdural space either through a skull bolt or via an open procedure. Various technologies are available: fibre-optic catheters where a change of ICP causes a change in the reflection of a light beam; catheter with a miniature strain gauge pressure sensor at the tip where a change of ICP causes a change in electrical resistance, and catheter using pneumatic technology where any pressure change is sensed by a small air pouch balloon at the end of the catheter. The advantages of microtransducer systems include ease of use, reliability, and low infection and procedure-related complication rates. A major drawback is that there exists a small zero drift of the sensor with time, although in vitro testing revealed a minor drift of 0.6 ± 0.9 mmHg after 5 days of use. The system also does not allow in vivo calibration. Another important disadvantage is that the probe measures only the local pressure, which may not reflect the true ICP as intracranial pressure gradients can exist in TBI. This begs the question of the ideal position of the probe. In diffuse brain injury, there should not be any differences in the hemispheric ICPs. If there is a significant focal lesion, ICP should be monitored on the same side as the lesion, or bilaterally if...
possible. Subarachnoid and epidural monitoring devices are available, but they are rarely used now due to limited accuracy of the devices. Lumbar CSF pressures are no longer monitored due to the lack of reliability of the ICP estimate and due to the inherent dangers in the presence of increased ICP. Non-invasive methods of ICP monitoring have also been developed. Sonographic measurement of the optic nerve sheath, sonographic monitoring of cranial diameter pulsations, measurement of tympanic membrane displacement by impedance audiometry, and CT (computer tomography) scan classification of ICP are explored but none of these have been conclusively useful in the clinical setting as yet. Table 1 summarises the various commonly used modalities for ICP monitoring.

The measurement of ICP provides a number of additional clinical information such as the analysis of ICP waveforms and the calculation of secondary indices (CPP, pressure reactivity index and pressure volume compensatory reserve). CPP is the difference between mean arterial blood pressure (MAP) and ICP. It is easily performed, is easily monitored continuously, and it is the most widely used surrogate for cerebral blood flow (CBF) estimation. As a result, CPP is used as a therapeutic target in many units. The BTF includes CPP in its management guidelines. There is much controversy surrounding the decision on the optimal CPP threshold. Rosner et al stressed an aggressive approach to CPP management, even advocating a CPP of 80mmHg or more. On the other hand, the Lund approach advocates a lower CPP: as low as 50mmHg as long as ICP is normal. The current BTF Guidelines recommend a CPP threshold of 60mmHg. The purpose of maintaining CPP at a certain threshold is to improve CBF at at-risk cerebral regions. However, CBF can improve with an increase in CPP only if autoregulation is impaired or if CPP is below the lower limit of autoregulation. Autoregulation curve can be shifted to the right after brain injury; it is also frequently disrupted or even completely abolished in TBI. Cerebral autoregulation may also be preserved in TBI patients, and this is advantageous as ICP can be reduced with the autoregulation-mediated compensatory vasoconstriction response. Using perfusion CT imaging, Wintermark et al showed that in some patients, CBF was in the ischaemic range in spite of a high CPP, and also that the extent of disruption of autoregulatory function cannot be elucidated just from baseline measurements of CPP and CBF. Thus, the state of cerebral autoregulation becomes a heterogeneous spectrum of adaptive changes in the cerebrovascular resistance in response to changes in the perfusion pressure throughout all regions of the brain. Moreover, inappropriately high CPP can result in complications.
such as acute respiratory distress syndrome\textsuperscript{32} and poorer outcomes\textsuperscript{19}. Different regions of the brain have different susceptibilities to ischaemic stress due to that fact that the state of autoregulation and CBF requirements differ between normal and injured brain tissue. Because of this, it is difficult to pinpoint the optimal threshold of CPP for management of TBI patients, and this threshold may vary from patient to patient, and may vary over time. Hence, an individualised approach to CPP management may be prudent\textsuperscript{27}. Thus far, there have not been any randomised clinical trials involving ICP monitoring and ICP- or CPP-directed therapy; the question whether these improve outcome is still unanswered. Irrespective of this fact, a meta-analysis by Stein \textit{et al}, reviewing trials and case series reported after 1970 comparing the patients with and without ICP monitoring and intensive treatment, showed that there was a significantly lower mortality rate (12\%) in the group with intensive therapy and a higher rate (6\%) of favourable outcome, and this was independent of temporal effects on treatment\textsuperscript{34}.

The pressure reactivity index (PRx) is a measure that reflects the state of pressure autoregulation of the cerebral vasculature. This index can be derived from calculating a moving correlation coefficient between spontaneous slow wave fluctuations in ICP and MAP\textsuperscript{35}, with the value of the index between -1 and 1. A negative PRx indicates a cerebral vasculature with intact pressure autoregulation whereas a positive PRx indicates a defective autoregulatory vasomotor system. An abnormal PRx is associated with a poor prognosis in TBI\textsuperscript{19,36}. A high mortality rate of >50\% was found with a PRx of >-0.3535. PRx is also found to correlate well with transcranial Doppler ultrasound assessment of cerebrovascular autoregulation\textsuperscript{36}. Zweifel suggested using PRx as a global measure of cerebrovascular reserve for vasomotor reactivity\textsuperscript{36}. PRx can be continuously monitored at the bedside\textsuperscript{19,27}. It has been suggested that the monitoring of PRx can be used to derive individualised CPP thresholds\textsuperscript{35–37}, and this should allow for optimal CBF.

**BRAIN OXYGENATION**

Maintaining an optimal level of cerebral oxygenation has long been recognised as an important component of the strategy in the management of TBI\textsuperscript{8,9,38}. There is evidence that ischaemia accounts for much of cellular damage in brain injury\textsuperscript{8}. Ischaemia can occur at early and late stages of brain injury. Furthermore, cerebral ischaemia can be induced with excessive hyperventilation\textsuperscript{39}, highlighting the importance of monitoring for ischaemia and making appropriate therapeutic modifications, e.g. adjustment of mechanical ventilation, to prevent or minimise secondary brain injury in the intensive care setting. CPP has conventionally been used as a marker for CBF in monitoring for cerebral ischaemia. However, as mentioned earlier in this article, the use of CPP is highly controversial, attracting much criticism\textsuperscript{8}. In addition, monitoring CBF alone may not be enough as there is much heterogeneity in cerebrovascular responses and metabolic demands in both injured and uninjured regions of the brain; areas with high metabolic demand may be ischaemic even with normal CBF, while low CBF may suffice for areas with decreased metabolic demand\textsuperscript{8}. Pathologic changes in ICP and CPP are not always responsible for secondary insults to the brain\textsuperscript{40}. Despite the best efforts to resuscitate using well-established ICP/CPP protocols, cerebral hypoxia is not consistently prevented\textsuperscript{40} and there has not been a palpable improvement in clinical outcome, albeit a decrease in mortality\textsuperscript{41}. Modalities that are currently available for monitoring cerebral oxygenation include jugular venous saturation ($S_{jvO_2}$) monitoring (assesses global brain oxygenation invasively), brain tissue oxygen tension ($P_{btO_2}$) monitoring (assesses focal brain oxygenation invasively), and near infrared spectroscopy (NIRS) monitoring (assesses regional brain oxygenation noninvasively). Table 2 summarises a comparison of these modalities.

**Jugular Venous Oxygen Saturation Monitoring**

The use of $S_{jvO_2}$ monitoring as an indirect measurement of cerebral oxygenation has been in place since the 1980s\textsuperscript{42,43}. Its clinical role in the assessment of global cerebral ischaemic and hyperaemic states as well its value in prognostication for TBI has been well-established\textsuperscript{8}. This technique involves the retrograde insertion of a catheter into the internal jugular vein (IJV) via a central approach. The catheter tip is positioned in the jugular bulb, and this is confirmed by the tip being seen at the level of the mastoid process (or at the lower border C1 vertebra) on a lateral neck X-ray\textsuperscript{42}. The UV with dominant drainage is usually catheterised as the monitored $S_{jvO_2}$ will then accurately reflect the global brain oxygenation\textsuperscript{44}. The dominant UV can be ascertained by manual compression of each IJV.
Table 2. Characteristics of modalities of cerebral oxygenation monitoring and microdialysis.

| Modality               | Advantages                                                                 | Disadvantages                                                                 |
|------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Jugular venous oxygen saturation | ▪ Global measure of cerebral oxygenation; lowly sensitive but highly specific in detecting ischaemia  
▪ Allows continuous, real-time $S_jV\text{O}_2$ monitoring and intermittent jugular venous blood sampling to assess cerebral oxygenation at bedside  
▪ Most established method of assessment of cerebral oxygenation  
▪ Relatively low-cost | ▪ Invasive method  
▪ Insensitive to detection of focal area of ischaemia  
▪ Venous sample may not be representative of entire brain if venous drainage is asymmetric  
▪ Extracerebral contamination of jugular bulb blood  
▪ Erroneous reading due to migration of catheter tip, head position, microthrombi at tip  
▪ Limited time of use  
▪ Frequent calibration needed  
▪ Limited value in monitoring of infratentorial injuries as brainstem and cerebellum contribute little to jugular venous outflow |
| Brain tissue oxygenation | ▪ Measure of focal cerebral oxygenation  
▪ Continuous, real-time measure at bedside  
▪ Good accuracy with few artefacts  
▪ Low post-procedure complication rate | ▪ Invasive method  
▪ Does not reflect global cerebral oxygenation  
▪ Position of probe crucial as it only measures focal oxygen tension  
▪ Measurement influenced by many factors, including ischaemic factors affecting oxygen delivery, arterial $p\text{O}_2$, and tissue barriers to oxygen diffusion  
▪ Interpretation of $P_{bt}\text{O}_2$ is complex due to the many factors affecting the measurement; no consensus on managing $P_{bt}\text{O}_2$ |
| Near-infrared spectroscopy | ▪ Non-invasive method  
▪ Continuous, real-time measure at bedside  
▪ Measures regional cerebral oxygenation; simultaneous monitoring with multiple probes allow estimation of global cerebral oxygenation | ▪ Difficulty in determining precise reference ranges and thresholds for hypoxia/ischaemia, due to: marked variability in baseline values of cerebral tissue oxygen saturation; and lack of standardisation of NIR monitors, algorithms and measured variables used by different devices  
▪ Signal significantly affected by extracerebral factors e.g. haematoma, cerebral swelling, subdural air  
▪ Least established of the 3 methods |
| Microdialysis | ▪ The only modality that permits monitoring of brain tissue biochemical markers, which indicate secondary brain injury, in local tissue  
▪ Continuous measure at bedside | ▪ Invasive method  
▪ Only focal measurement, so probe position is crucial (usually placed in penumbra zone of focal traumatic lesion)  
▪ Does not reflect global condition of the brain  
▪ Normal range of values for biochemical markers not well-established; range may be highly individualized, so only trend data is useful  
▪ Not well established as clinical monitoring modality; still used as research tool in many centres |
(the compressed IJV causing the larger ICP increase is the dominant one), CT identification of the larger jugular foramen, or by sonographic comparison of the sizes of both IJVs. If it is not able to be determined, the right UV is usually presumed to be the dominant side. It has been shown that the difference between the SjvO2 measured from both IJVs can be >10% in a large proportion of patients. SjvO2 can be measured by using a co-oximeter on a blood sample drawn from the jugular bulb, or it can be continuously determined by fibreoptic oximetry. The normal range for SjvO2 is 55 to 75%. Ischaemic cerebral blood flow is considered to occur when SjvO2 is low, and this can be due to hypoxaemia, inadequate CBF from various causes (e.g. excessive hyperventilation, reduced CPP and vasospasm), or increased cerebral metabolism (CMRO2). In TBI, a SjvO2 of <50% is associated with vasospasm, hyperaemia is believed to be attributed to a defective cerebral autoregulatory system and is predictive of a poor outcome. A high SjvO2 from decreased cerebral metabolism is a stronger predictor of a poor outcome compared to hyperventilation. Indeed, with its ability to monitor the balance between oxygen delivery and utilisation in real time, SjvO2 monitoring provides a range of clinical applications: it allows detection of cerebral ischaemia, guides hyperventilation therapy, and allows optimisation of CPP and fluid management. The harm of cerebral hypoperfusion from excessive hyperventilation cannot be stressed enough, and guidance from SjvO2 monitoring can help achieve “optimal hyperventilation” in the management of TBI. SjvO2 monitoring does have significant limitations. SjvO2 is a global measure of cerebral oxygenation; it has a low sensitivity but high specificity in detecting ischaemia. It is rather insensitive to the detection of focal areas of ischaemia, and it has a poor correlation with measurements of PbTO2 in areas of focal lesions in TBI. Coles et al used positron emission tomography (PET) to demonstrate that SjvO2 <50% was only achieved after 13 ± 5% of brain tissue volume became ischaemic. This relative insensitivity to regional ischaemia has contributed to the controversy of the site of SjvO2 monitoring. In cases with focal lesions, some will recommend monitoring the ipsilateral side as about 70% of cerebral venous blood drain into the ipsilateral UV; in cases with diffuse lesions, the dominant UV is cannulated. On the other hand, some advocate cannulating the dominant UV in all cases. Another limitation is the presence of extracerebral contamination of the jugular bulb blood sample; blood from the scalp, skull and meninges accounts for 3% of jugular bulb blood. Erroneous readings due to migration of the tip of the catheter are also a common problem, and frequent calibration is needed. A few SjvO2-derived indices have been evaluated. Arterio-jugular difference of oxygen content (AJDO2) is the ratio of CMRO2 to CBF and has been used as a global measure of cerebral oxygenation. Stocchetti et al showed that a low AJDO2 was associated with a poor outcome while normal or high AJDO2 was indicative of a better prognosis. Cerebral lactate level is believed to correlate with degree of brain injury and prognosis. Poca et al showed that arteriojugular differences of lactate did not correlate with cerebral tissue lactate levels and could not be relied on to rule out cerebral ischaemia. Despite the relatively long history the use of SjvO2 monitoring, there has been no evidence that it impacts on patient outcome.

**Brain Tissue Oxygenation Monitoring**

Maintenance of adequate cerebral oxygenation is the main goal in the management of TBI. PbTO2 monitoring has proven to be an increasingly important component in the armamentarium of monitors used in neurocritical care. There have been many studies investigating the role of PbTO2 monitoring in TBI and strategies for PbTO2-directed therapy have been developed. PbTO2 monitoring was introduced in the BTF guidelines in 2007. PbTO2 can be monitored using microprobes that are invasively placed in the brain tissue of interest. Three commercially available systems are developed: Licox(IntegraNeurosciences, Plainsboro, NJ, USA), Raumedic (Raumedic AG, Germany), and Neurotrend (Codman, Raynham, MA, USA); the Neurotrend is no longer available. There has been much debate of what PbTO2 measures. It is conceivable as a measure of the equilibrium between oxygen supply and demand.
in brain tissue. It is also reasonable to consider it as a reflection of the balance of the factors that influence the perfusion and diffusion of oxygen through brain tissue. These factors include arterial partial pressure of oxygen, arterial partial pressure of carbon dioxide, haemoglobin level, ICP, CPP, CBF, and tissue barriers to diffusion. Pathologic processes, such as perivascular oedema, cytotoxic cell swelling, arteriovenous shunting and microvascular collapse, can impair the diffusion of oxygen through brain tissue and thus affect PbtO2 levels. It has been shown that PbtO2 correlates with the product of CBF and arteriovenous difference in oxygen tension, thus a low PbtO2 value may be more indicative of impaired oxygen diffusion instead of reduced oxygen supply or metabolism. The normal PbtO2 is thought to be in the range of 25 to 30 mmHg. Prognosis worsens as PbtO2 progressively decreases below 20mmHg. The critical threshold of 10mmHg is considered to be "hypoxic" and is strongly associated with neuronal injury and poor outcome. Stiefel et al. found that hypoxic PbtO2 levels still occurred despite adequate resuscitation of TBI patients (ICP <20mmHg and CPP >60mmHg). Derangements of markers of cerebral ischaemia through microdialysis assessment are associated with decreased PbtO2 levels. PbtO2 of 20 to 25 mmHg has been suggested as a threshold for therapeutic intervention as the range 15 to 20 mmHg represents reduced oxygenation. Spiotta et al. reported that mortality was associated with lower mean daily PbtO2, longer durations of decreased PbtO2 (<20mmHg), and more episodes and longer cumulative duration of decreased PbtO2. Any occurrence of PbtO2 <6mmHg is also highly predictive of mortality.

As with ICP- and CPP-directed therapy, there is lack of robust evidence as to whether PbtO2-directed therapy improves outcome. A systematic review by Maloney-Wilensky et al. analysed clinical studies on PbtO2 monitoring in severe TBI published between 1993 and 2008. There were no randomised clinical trials and only 3 studies met the inclusion criteria for analysis. The results indicated that brain hypoxia correlated with worse outcome, and implied that outcome might be improved if therapy to increase PbtO2 was instituted. Meixensberger et al. showed a tendency, without statistical significance, for a better outcome in TBI patients who received PbtO2-directed therapy compared with those who received ICP/CPP-directed therapy. Stiefel et al., Narotam et al. and Spiotta et al. reported that there were significant reductions in mortality rate in TBI patients who underwent PbtO2-directed treatment in comparison with those who underwent conventional ICP/CCP-directed treatment. Spiotta et al. also found that outcome was worse for patients who responded poorly to treatment to improve PbtO2. However, in these 3 studies, the mortality rates for patients who received ICP/CCP-directed therapy were higher than expected from mortality rates reported in some clinical studies on TBI. A mortality rate of 36% was reported from analysis of data on severe TBI extracted from the Traumatic Coma Data Bank. On the other hand, Martini et al. found that the mortality rate for patients who had PbtO2-directed therapy was higher, and that PbtO2 monitoring might be associated with worse neurological outcome. However, a major limitation of the study was that the baseline prognostic characteristics of the 2 groups of patients were markedly different. Besides optimising CBF, CPP, ICP and haemoglobin concentrations, increasing oxygen delivery to injured brain tissue by increasing fraction of inspired oxygen (FiO2) and PaO2 has been investigated. There is some evidence that PbtO2 increases with increased inspired oxygen, and this is associated with improvement in biochemical markers of metabolism. However, a recent review found that studies using PET to investigate the influence of hyperoxia on cerebral oxygenation did not find an improvement in oxygen utilisation by the brain. Hlatky et al. found that the increase in PbtO2 by hyperoxia therapy was small in brain regions where the CBF was <20ml/100g/min when compared to the regions where the CBF was >20ml/100g/min, and concluded that the regions of the brain that would most likely benefit from increased oxygen delivery were the least likely to have improved PbtO2. A recent randomised clinical trial showed that increasing the dissolved cerebral oxygen concentration by using hyperbaric oxygen therapy could achieve an improvement in oxidative cerebral metabolism and reduction in ICP, but a PbtO2 of ≥20 mmHg was required for a significant effect.

PbtO2 monitoring is safe and has low rates of infection and post-insertion hematoma formation. The main limitation of PbtO2 is that it measures only focal brain oxygenation, and it does not necessarily reflect global brain oxygenation.
Although it has been established that low PbtO₂ is problematic, ScO₂ readings can be challenging to the clinician. The monitor helps in understanding how the balance between the components of the tissue in the field of view of the probe is affected. ScO₂ reflects the balance between the components of the tissue in the field of view of the probe, and its attenuation is influenced by many factors as elucidated earlier. Besides ischaemic factors, pathologic changes affecting diffusion of oxygen through brain tissue as well as PaO₂ do influence PbtO₂. As such, interpretation of any change in PbtO₂ readings can be challenging to the clinician. Although it has been established that low PbtO₂ is associated with poor outcomes, further research is needed to investigate whether PbtO₂-directed therapy benefits patients.

Near-infrared Spectroscopy (NIRS)

NIRS is a non-invasive technique that can be used to continuously monitor cerebral oxygenation over multiple regions of the brain. This technique is based on the transmission and absorption of near-infrared electromagnetic radiation (700 to 1,000 nm) at various wavelengths as it passes through tissue, and the principle behind this is that near-infrared radiation penetrates tissue well and its attenuation is influenced by many factors. As oxygen and deoxyhaemoglobin have different absorption spectra, cerebral oxygenation can be estimated from their relative absorption of near-infrared radiation. Factors that can affect the absorption include skull thickness, myelin sheath, cerebrospinal fluid, ambient light and changes in extracranial blood flow. The development of analysis of NIRS signals has seen progress from simple continuous wave analysis to time-resolved analysis (time or frequency domain) to spatially resolved techniques. Early monitors allow only trend monitoring of changes in concentrations of tissue chromophores, but technical advances in spatially resolved spectroscopy have enabled absolute measurements of cerebral tissue oxygen saturation (ScO₂), which is a composite of oxygen saturation of arterial, venous and capillary components of the tissue in the field of view of the monitor. ScO₂ reflects the balance between cerebral oxygen supply and utilisation. Attempts have been made to define normal values for ScO₂ and the thresholds at which hypoxia/Ischaemia occurs. Some have concluded that it is difficult to ascertain precise reference ranges and thresholds for hypoxia/Ischaemia. One contributing factor is that there is marked variability in the baseline values of ScO₂. The normal range of ScO₂ is thought to be between 60 to 75% with a variation in baseline values of up to 10% and hypoxic/ischaemic thresholds are likely to be individual and disease-specific. Definition of thresholds is also made harder by the lack of standardisation of the commercially available NIRS monitors, the different algorithms and measured variables used by the various devices, and the resulting limitations of comparing the various devices and their corresponding studies. The tissue oxygen index (TOI) ratio of oxygenated to total tissue haemoglobin was used in patients who underwent carotid endarterectomy in an attempt to define a threshold for ischaemia. Cerebral ischaemia after carotid clamping was detected by the use of electroencephalography (EEG), and it was suggested that a decrease of 13% from the baseline TOI signalled a threshold for cerebral ischaemia. Kurth et al showed that at a hypoxic ScO₂ level of 35% for more than 2 hours in a piglet model, the incidence of permanent neurological damage progressively increased at a rate of 15% every hour, and this was heralded by abnormalities in NIRS variables during reperfusion. ScO₂ level of 35% lasting for less than 2 hours was not associated with any significant neurological deficit. These findings suggest that a viability-time threshold for hypoxic brain injury using ScO₂ can be defined; that NIRS can be used to prognosticate; and that there exists a window period of a few hours following the onset of ischaemia/hypoxia for intervention to prevent or minimise neurological injury. It is also possible to measure changes in the concentrations of cytochrome c oxidase (CCO), which is the terminal complex of the electron transfer chain in mitochondria. This has been validated in animal studies as an assessment of cellular energy status. Thus, CCO brings forth a potential for evaluation of intramitochondrial redox state as well as sufficiency of cerebral oxygen supply and utilisation in TBI. Newer NIRS devices have been adapted to measure CCO continuously, and CCO measurements using NIRS have been used to show increased oxidation state of cerebral mitochondria after normobaric hyperoxia. One major limitation of NIRS is that its signal can be significantly affected by extracerebral factors. NIRS can be rendered less accurate in TBI, due to factors such as haematoma collections, cerebral swelling, subdural air collection and a wet chamber between the skin and the optode. These problems have been considerably addressed with...
the use of spatially resolved spectroscopy, which has been demonstrated to have high sensitivity and specificity to intracranial oxygenation changes\textsuperscript{75}, and it has been evaluated against SjvO\textsubscript{2} and PbtO\textsubscript{2} measurements in response to normobaric hyperoxia in patients with TBI\textsuperscript{76}. Indeed, CCO measurements by NIRS tend to be less susceptible to extracerebral contamination as the concentration of mitochondria in the brain is higher than other tissue in the human body\textsuperscript{70}. Currently available NIRS systems involve the placement of optodes on the forehead, allowing assessment of regional cerebral oxygenation, and this limits the detection of cerebral oxygenation in sites distant to the optodes. Now, multiprobe NIRS devices allow simultaneous monitoring of multiple regions, hence giving a more global assessment of cerebral oxygen sufficiency\textsuperscript{48,70}. As of now, amid conflicting reports on the efficacy of NIRS\textsuperscript{48}, there has not been any randomised clinical trial to ascertain the clinical efficacy of NIRS in TBI, and there has not been any study to evaluate NIRS-directed therapy on outcome in TBI.

**BRAIN NEUROCHEMISTRY**

Cerebral microdialysis was first introduced for laboratory use in the 1960s before gaining popularity for clinical monitoring of neurochemistry in the intensive care unit in the 1990s\textsuperscript{77–80}. The principles of cerebral microdialysis have been succinctly described in another review\textsuperscript{79}. Monitoring cerebral tissue biochemistry offers the opportunity for timely detection of impending or early onset secondary brain injury, hence permitting judicious application of neuroprotective techniques. The cascade of pathological processes set off in secondary brain injury leads to changes in cerebral metabolism and brain cell damage. This can be reflected as a change in the biochemical milieu in cerebral tissue\textsuperscript{79}. Just as with PbtO\textsubscript{2} monitoring catheters, the importance of microdialysis catheter location has been highlighted. It has been demonstrated that microdialysis analyte measurements from the penumbra zone of focal traumatic lesions and those from normal brain tissue ipsilateral and contralateral to the side of the traumatic lesion differ significantly\textsuperscript{81}. Thus, by placing the microdialysis catheter in the at-risk penumbra zone of focal traumatic lesions, neurochemical changes due to secondary insults in the region of the brain most susceptible to injury can be measured\textsuperscript{79}. A second probe can be placed in normal brain tissue if needed\textsuperscript{80}. It is recommended that the catheter be placed in the right frontal lobe in the case of diffuse injury\textsuperscript{80}. The most commonly measured microdialysis analytes include glucose, lactate, pyruvate, glutamate and glycerol\textsuperscript{2,79,80}. Information on bioenergetic sufficiency or the lack of it is provided by measurements of glucose, lactate, pyruvate and glutamate\textsuperscript{80}. Microdialysis glutamate levels also reflect the excitatory amino acid activity in the injured brain\textsuperscript{80}. Glycerol is released after enzymatic degradation of cell membrane phospholipids during failure of cellular metabolism, and hence is a marker of cell damage\textsuperscript{2,80}. A summary of the characteristics of microdialysis is presented in Table 2.

Glucose is the main substrate for cellular metabolism in the brain. After TBI, microdialysis glucose levels typically decrease, and a concentration blow 0.66mmol/L in the first 50 post-TBI hours is related to a worse prognosis\textsuperscript{82}. However, the correlation between ischaemia and low microdialysis glucose levels is poor\textsuperscript{82,83}, intimating the likelihood that low microdialysis glucose levels may be related to hyperglycolysis rather than ischaemia\textsuperscript{79}. The relative concentrations of microdialysis lactate and pyruvate reflect the extent of cerebral anaerobic metabolism. The microdialysis lactate-pyruvate ratio (LPR) is considered a more dependable and robust indicator of cerebral tissue ischaemia when compared to lactate alone\textsuperscript{79}. Thus, the LPR is the most widely used microdialysis indicator of ischaemia and is typically markedly increased in severe brain tissue ischaemia/hypoxia, with an elevated LPR greater than the threshold of 20 to 25 associated with a worse prognosis\textsuperscript{2,79}. LPR has been correlated with regional oxygen extraction fraction measured with PET\textsuperscript{84}. Although LPR has been conventionally used as a marker of ischaemia, it is found that it is not as specific for ischaemia as previously thought; there is evidence that markedly raised LPR is found in the absence of ischaemia and this may be the result of failure of mitochondria to utilise delivered oxygen\textsuperscript{83,85}. Increased LPR has been classified: Type 1 reflects the conventional ischaemic metabolic state, in which microdialysis lactate is increased while pyruvate is decreased; the nonischaemic raised LPR is designated as Type 2, in which a decreased microdialysis pyruvate is the prime feature\textsuperscript{79}. The Type 2 anomaly may be a result of a failure in the glycolysis process or an inadequacy of glucose as a substrate due to shunting of glucose to other pathways like the pentose phosphate pathway\textsuperscript{80,86}. Marcoux et al\textsuperscript{87}
showed that persistent metabolic crisis, as indicated by increased LPR, was predictive of the extent of frontal lobe atrophy at six months, and that the percentage of time of elevated LPR correlated with the extent of frontal lobe atrophy, but not with global cerebral atrophy. Thus, microdialysis LPR has the potential to be a clinically useful but nonspecific indicator of metabolic distress in brain tissue.

It has been demonstrated that hyperglycaemia is associated with a poorer outcome in critically ill patients, and hence there has been interest in rigorous glycaemic control using insulin in patients with severe TBI. Vespa et al. compared the effects of intensive insulin therapy and a more relaxed insulin regime and found that there was a significantly greater decrease in microdialysis glucose levels in the intensive insulin therapy group (70% vs 15%). The intensive group was also associated with a higher microdialysis glutamate level and an increased microdialysis lactate/pyruvate ratio, but there was no difference in mortality in both treatment groups. Oddo et al. compared 2 treatment regimes in critically ill patients: a “tight” glycaemic control group (blood glucose kept at 4.4–6.7 mmol/L) and an “intermediate” control group (blood glucose at 6.8–10.0 mmol/L). There was a significantly greater prevalence of low microdialysis glucose (65% vs 36%) and brain energy crisis (defined as microdialysis glucose <0.7mmol/L and lactate/pyruvate ratio >40; 25% vs 17%) in the tight glycaemic control group. Brain energy crisis was independently predicted by systemic glucose level and insulin dose, after adjusting for ICP and CPP. Non-survivors had lower microdialysis glucose concentrations compared to survivors, and there was a higher mortality rate associated with brain energy crisis.

Glutamate is the major excitatory amino acid in cerebral tissue. Excessive release in TBI may cause excitotoxicity, which is a form of secondary neurotoxic insult to the brain. Injury can occur as a result of excessive calcium and sodium influx through glutamate-mediated ion channels, mitochondrial dysfunction, and dendritic morphological changes culminating in cell death by delayed apoptosis or rapid necrosis. Increased extracellular glutamate in the brain has been observed after cerebral ischaemia and TBI, and has been correlated with high ICP and poor prognosis. A moderate increase in microdialysis glutamate may signify reversible ischaemia; markedly elevated glutamate levels associated with an increased microdialysis glycerol can be a sign of irreversible neuronal damage. Chamoun et al. found that there was a tendency for a higher mortality rate with a high initial microdialysis glutamate in the first 24 hours post-injury: 30% mortality rate in patients with microdialysis glutamate level >20µmol/L compared with 18% with level <20 µmol/L. Two patterns of changes in glutamate levels over time were described: in Pattern 1, glutamate levels tended to normalise over time, while glutamate levels tended to rise over time or remain abnormally high in Pattern 2. It was demonstrated that Pattern 1 was associated with a lower mortality rate (17.1% vs 39.6%) and a more favourable functional outcome (41.2% vs 20.7%). Microdialysis glutamate is considered a late marker of cellular distress and its clinical role in monitoring in TBI is still being investigated.

Glycerol is released into cerebral extracellular fluid space after degradation of cell membrane phospholipids during cerebral metabolic distress. Thus, it has the potential to be a clinically important marker of cerebral ischaemia/hypoxia. At present, there is a surfeit of evidence to validate its specificity for ischaemia/hypoxia. Glycerol from systemic sources as well as conversion from glucose may potentially contribute to the extracellular glycerol concentration. Clausen et al. investigated the relationships between cerebral extracellular glycerol, PbtO₂, CPP and outcome in a large cohort of 76 patients with severe TBI. It was found that the mean microdialysis glycerol concentration was typically raised during the first 24 hours post-injury, apparently the result of the primary injury, before an exponential decrease over the subsequent 3 days. Despite the finding that CPP <70mmHg and PbtO₂ <10mmHg correlated with increased mean microdialysis glycerol, individual episodes below the same thresholds without a concomitant increase in microdialysis glycerol were often observed. Moreover, there was no significant difference in the mean microdialysis glycerol concentrations between patients with favourable and unfavourable outcomes. Another study failed to demonstrate any association between microdialysis levels and secondary clinical events like elevated ICP and decreased CPP. These results suggest that more work is needed to validate the clinical value of microdialysis glycerol. Other microdialysis analytes have also...
been investigated: cytokines\textsuperscript{80,94}, nitric oxide metabolites\textsuperscript{80,95}, N-acetylaspartate\textsuperscript{80} and amyloid proteins\textsuperscript{96}. At present, evidence for their clinical use is lacking.

Post-traumatic seizures have been recognised to occur frequently in TBI patients\textsuperscript{97}. It is not until recent years that a high frequency of non-convulsive seizures and non-convulsive status epilepticus is detected with the use of continuous electroencephalography\textsuperscript{80,98}, and an increased mortality rate is associated with prolonged status epilepticus\textsuperscript{98}. Post-traumatic seizures have been associated with increased levels of microdialysis glutamate\textsuperscript{99}. It has also been demonstrated that non-convulsive seizures detected with electroencephalography is associated with increased ICP and raised microdialysis LPR, suggesting that seizures can result in or worsen intracranial hypertension, and can potentiate cerebral metabolic distress, which can result in permanent cellular injury, hence making post-traumatic seizures an important target for treatment\textsuperscript{98}. Cortical spreading depolarisation (CSD) was previously thought to be benign but is now found to be a common and potentially pathogenic phenomenon in TBI\textsuperscript{80}. Using rapid sequence microdialysis, Hashemi et al\textsuperscript{100} showed that there was significant decrease in glucose concentration and increase in lactate concentration during the hyperaemic phase of CSD, and the degree of depression of glucose was proportional to the number of depolarisations. The authors suggested that a vicious cycle can be set off, in which CSDs triggering glucose depletion and metabolic distress may lead to more CSDs, until terminal depolarisation ensues.

Microdialysis has been used to investigate the effects of hypothermia in critically ill patients. In a study on TBI patients, changes in brain neurochemistry suggested that mild hypothermia provided neuroprotection: microdialysis LPR, lactate-glucose ratio (LGR) and glycerol concentrations in perilesional tissue and LPR in “normal” cerebral tissue decreased with hypothermia. In comparison, the LPR, LGR and glycerol levels in perilesional tissue were higher than those in “normal” tissue during normothermia\textsuperscript{80}.

As discussed in an earlier part of this review, there is interest in normobaric hyperoxia therapy in TBI. Tisdall et al\textsuperscript{74} demonstrated that with FiO\textsubscript{2} of 100%, there were an increase in PbtO\textsubscript{2} of 7.2kPa, a decrease in microdialysis lactate concentration of 0.26mmol/L, a decrease in microdialysis LPR of 1.6 and an increase in oxidised cytochrome c oxidase concentration of 0.21μmol/L. No significant changes in ICP or arterial or microdialysis glucose were found. The authors concluded that the findings were consistent with increased aerobic metabolism and that normobaric hyperoxia can potentially improve clinical outcome in TBI. On the other hand, Nortje et al\textsuperscript{101} compare the effects of hyperoxia (FiO\textsubscript{2} increases between 0.35 and 0.5) and normoxia on microdialysis parameters, PbtO\textsubscript{2} and oxygen-15 PET and found that hyperoxia significantly increased mean PbtO\textsubscript{2} from 28 ± 21 mmHg to 57 ± 47 mmHg while there were no changes in microdialysis lactate and pyruvate levels. There was a statistically significant decrease in microdialysis LPR in the hyperoxia group (32.5 ± 9.0 vs 34.1 ± 9.5) but the authors doubted the clinical significance of the result. In view of the potentially deleterious clinical effects of hyperoxia, hyperoxia therapy is not recommended as a form of standard treatment for TBI at present\textsuperscript{67}.

Although tentative normal values for the most commonly monitored microdialysis analytes (glucose, lactate, pyruvate, glutamate and glycerol) has been described\textsuperscript{79,102-103}, one must understand that values for these analytes do vary significantly over time post-injury within the individual patient, and there are wide inter-individual variations in these values too\textsuperscript{77,79}. As interpretation of an analyte measurement in isolation may prove to be difficult, microdialysis is probably best used for trend monitoring, and interpretation should be made in context with other modes of monitoring. There has been much research into how the use of cerebral microdialysis can impact on clinical decision-making. As discussed above, microdialysis may be useful as a prognostic indicator. Microdialysis may also be useful in directing hyperventilation therapy\textsuperscript{104}, guiding management of CPP\textsuperscript{105} as well as influencing the decision for decompressive craniectomy\textsuperscript{79}. There has been an ever-expanding amount of information provided by the use of cerebral microdialysis in TBI, and there is accumulating evidence advocating its routine use in the clinical setting. However, there is an absence of level one evidence demonstrating its clinical value at present, and more prospective trials are needed to address this. Nonetheless,
cerebral microdialysis has the potential to be an integral part of the routine multimodal monitoring armamentarium in the management of TBI.

CONCLUSION
The purpose of neuromonitoring in TBI is the early detection of pathological insults which can lead to secondary brain injury and subsequent permanent brain cell death, ultimately resulting in a poor clinical outcome. A mode of monitoring is only useful if it allows timely detection and identification of an insult, if it can influence a management decision, and/or if it can provide a reasonably accurate prognosticating function. The principles of neuromonitoring are based on the assumption that there is an unequivocal link between secondary cerebral injury and a worse clinical outcome. In addition, the clinical significance of the monitored clinical event with reference to outcome has not been firmly established. Whether an intervention appropriate for an abnormal event exists, and if so whether the intervention will influence outcome remain pertinent questions. Monitoring on its own does not improve outcome if it does not lead to effective therapeutic management. At present, there is a lack of level one evidence for each mode of neuromonitoring. Despite this, multimodal monitoring does provide the clinician with wide array of useful information which can potentially assist in clinical decision-making. The challenge is the integration and analysis of this array of information which allows the generation of a reasonable and appropriate management plan. The clinician should develop the techniques of assimilation of vast amount of data, and not be intimidated by the inundation of information. Multimodal monitoring is probably best utilised as a tool to better understand the pathophysiological processes occurring in the individual TBI patient, and hence allow the clinician to form a customised management strategy for the individual patient rather than depend on a rigorous therapeutic regime aimed at achieving standard physiological targets. Coupled with future technological advances and development of software that assists the clinician in integration and interpretation of monitored parameters, this approach likely holds the promise of improving clinical outcomes of TBI patients.

REFERENCES
1. Marshall LF. Head injury: recent past, present, and future. Neurosurgery. 2000;47(3):546–61.
2. Tisdall MM, Smith M. Multimodal monitoring in traumatic brain injury: current status and future directions. Br J Anaesth. 2007;99(1):61–7.
3. Chestnut RM. Secondary brain insults after head injury: clinical perspectives. New Horiz. 1995;3(3):366–75.
4. Chestnut RM, Marshall LF, Klauber MR, Blunt BA, Baldwin N, Eisenberg HM, et al. The role of secondary brain injury in determining outcome from severe head injury. J Trauma. 1993;34(2):216–22.
5. Diedler J, Czosnyka M. Merits and pitfalls of multimodality brain monitoring. Neurocrit Care. 2010;12(3):313–6.
6. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24(Suppl 1):S37–44.
7. Hlatky R, Robertson CS. Multimodality monitoring in severe head injury. Curr Opin Anaesthesiol. 2002;15(5):489–93.
8. Vespa PM. Multimodality monitoring and telemonitoring in neurocritical care: from microdialysis to robotic telepresence. Curr Opin Crit Care. 2005;11(2):133–8.
9. Timofeev I, Gupta A. Monitoring of injured patients. Curr Opin Anaesthesiol. 2005;18(5):477–83.
10. Forsyth RJ, Wolny S, Rodrigues B. Routine intracranial pressure monitoring in acute coma. Cochrane Database Syst Rev. 2010 Feb 17;(2):CD002043.
11. Smith M. Monitoring intracranial pressure in traumatic brain injury. Anaesth Analg. 2008;106(1):240–8.
12. Narayan RK, Kishore PR, Becker DP, Ward JD, Enas GG, Greenberg RF, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. J Neurosurg. 1982;56(5):650–9.
13. Eisenberg HM, Gary HE Jr, Aldrich EF, Saydjari C, Turner B, Foulkes MA, et al. Initial CT findings in 753 patients with severe head injury. A report from the NIH Traumatic Coma Data Bank. J Neurosurg. 1990;73(5):688–98.
14. Juul N, Morris GF, Marshall SB, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. J Neurosurg. 2000;92(1):1–6.
15. Marmarou A, Anderson RL, Ward JD, Choi SC, Young HF, Eisenberg HM, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. J Neurosurg. 1991;75(Suppl 1):S59–66.
16. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Intracranial pressure thresholds. J Neurotrauma. 2007;24(Suppl 1):555–8.
17. Vik A, Nag T, Fredriksson OA, Skandsen T, Moen KG, Schirmer-Mikalsen K, et al. Relationship of “dose” of intracranial hypertension to outcome in severe traumatic brain injury. J Neurosurg. 2008;109(4):678–84.
18. Marshall LF, Marshall SB, Klauber MR, Berkum Clark M, Eisenberg HE, Jane JA, et al. A new classification of head injury based on computer tomography. J Neurosurg. 1991;75(Suppl 1):S14–20.
19. Steiner LA, Andrews PJD. Monitoring the injured brain: ICP and CBF. Br J Anaesth. 2006;97(1):26–38.
20. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES Jr. Ventriculostomy-related infections: a critical review of the literature. Neurosurgery. 2002;51(1):170–81.
21. Koskinen LO, Oliviacrona M. Clinical experience with the intraparenchymal intracranial pressure monitoring Codman MicroSensor System. Neurosurgery. 2005;56(4):693–8.
22. Martinez-Manas RM, Santamarta D, de Campos JM, Ferrer E. Camino™ intracranial pressure monitor: prospective study of accuracy and complications. J Neurol Neurosurg Psychiatry. 2000;69(1):82–6.
23. Sahuquillo J, Poca MA, Arribas M, Garnacho A, Rubio E. Interhemispheric supratentorial intracranial pressure gradients in head-injured patients: are they clinically important? J Neurosurg. 1999;90(1):16–26.

24. Del Castillo MA. Monitoring neurologic patients in injury using 15O PET imaging. Curr Opin Crit Care. 2001;7(2):49–60.

25. The Brain Trauma Foundation, The American Association of Neurological Surgeons, The Joint Section on Neurotrauma and Critical Care. Intracranial monitoring technology. J Neurotrauma. 2007;24(Suppl 1):S45–54.

26. Stocchetti N, Longhi L, Zanier ER. Intracranial pressure monitoring for traumatic brain injury: available evidence and clinical implications. Minerva Anestesiol. 2008;74(5):197–203.

27. White H, Venkatesh B. Cerebral perfusion pressure in neurotrauma: a review. Anesth Analg. 2008;107(3):979–88.

28. The Brain Trauma Foundation, The American Association of Neurological Surgeons, The Joint Section on Neurotrauma and Critical Care. Cerebral perfusion pressure thresholds. J Neurotrauma. 2007;24(Suppl 1):S59–64.

29. Johnsrude IS, Johnsrude AH. Cerebral perfusion pressure: management protocol and clinical results. J Neurosurg. 1995;83(6):949–62.

30. Mascia L, Andrews PJ, McKeating EG, Souter MJ, Merrick JD, et al. Defining ischemic burden after traumatic brain injury. Crit Care Med. 2002;30(4):733–8.

31. Wintermark M, Chioléro R, van Melle G, Revelly JP, Porchet N, Czosnyka M, Smielewski P, Timofeev I, et al. Continuous monitoring of arteriojugular venous differences of lactate as a reliable indicator of increased intracranial pressure and poor outcome analysis of a brain tissue oxygen-directed monitoring in traumatic brain injury and major trauma: outcome analysis of a brain tissue oxygen-directed therapy. J Neurosurg. 2009;111(4):672–82.

32. Schell RM, Cole DJ. Cerebral monitoring: Jugular venous oximetry. Anesth Analg. 2000;90(3):559–66.

33. De Deyne CSI, Struys MRF. New developments in cerebral monitoring. Curr Opin Anesthesiol. 2000;13(5):517–21.

34. Lam JM, Chan MS, Poon WS. Cerebral venous oxygen saturation monitoring: is dominant jugular bulb cannulation good enough? Br J Neurosurg. 1996;10(4):357–64.

35. Robertson CS, Narayan RK, Gokaslan ZL, Pahwa R, Grossman RG, Caram P Jr. Cerebral arteriovenous oxygen difference as an estimation of cerebral blood flow in comatose patients. J Neurosurg. 1989;70(2):222–30.

36. Beards SC, Yule S, Kassner A, Jackson A. Anatomical variation of cerebral venous drainage: the theoretical effect on jugular bulb blood samples. Anaesthesia. 1998;53(7):627–33.

37. Stocchetti N, Paparella A, Bridelli F, Bacchi M, Piazza P, Zuccoli P. Cerebral venous oxygen saturation studied with bilateral samples in the internal jugular veins. Neurosurgery. 1994;34(1):38–43.

38. Rohlwink UK, Figaji AA. Methods of monitoring brain oxygenation. Childs Nerv Syst. 2010;26(4):453–64.

39. Chieregato A, Calzolari F, Trasforini G, Targa L, Latronico N. Normal jugular bulb oxygen saturation. J Neurol Neurosurg Psychiatry. 2003;74(6):784–6.

40. Chan MT, Ng SC, Lam JM, Poon WS, Gin T. Re-defining the ischemic threshold for jugular venous oxygen saturation – a microdialysis study in patients with severe head injury. Acta Neurochir Suppl. 2005;95:63–6.

41. Gupta AK, Hutchison PJ, Al-Rawi P, Gupta S, Swart M, Kirkpatrick PJ, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. Anesth Analg. 1999;88(3):549–53.

42. Coles JP, Poca MA, Smielewski P, Chatfield DA, Steiner LA, Johnston AJ, et al. Incidence and mechanisms of cerebral ischemia in early clinical head injury. J Cereb Blood Flow Metab. 2004;24(2):202–11.

43. Stocchetti N, Canavesi K, Magnoni S, Valeriani V, Conte V, Rossi S, et al. Arterio-jugular difference of oxygen content and outcome after head injury. Anesth Analg. 2004;99(1):230–4.

44. Poca MA, Sahuquillo J, Villalta A, Garnacho A. Lack of utility of arteriojugular venous differences of lactate as a reliable indicator of increased brain anaerobic metabolism in traumatic brain injury. J Neurosurg. 2007;106(4):530–7.

45. Brain Trauma Foundation; American Association of Neurological Surgeons; The Joint Section on Neurotrauma and Critical Care. Guidelines for the management of severe traumatic brain injury: X. Brain oxygen monitoring and thresholds. J Neurotrauma. 2007;24(Suppl 1):S565-70.

46. Spiotta AM, Stiefel MF, Gracias VH, Garuffe AM, Kofre WA, Maloney-Wilensky E, et al. Brain tissue oxygen-directed management and outcome in patients with severe traumatic brain injury. J Neurosurg. 2010;113(3):571-80.

47. Menon DK, Coles JP, Gupta AK, Smielewski P, Chatfield DA, et al. Diffusion limited oxygen delivery compared with jugular venous oxygen saturation for optimizing cerebral perfusion pressure management and outcome in patients with severe head injury. Anesth Analg. 2009;109(3):495-503.

48. Grossman RG, Caram P Jr. Cerebral arteriovenous pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med. 2002;30(4):733–8.

49. Coles JP, Regional ischaemia after head injury. Curr Opin Crit Care. 2004;10(2):120–5.

50. Maloney-Wilensky E, Gracias V, Itkin A, Hoffman K, Bloom S, Yang W, Christian S, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. Crit Care Med. 2009;37(6):2057–63.
70. McLeod AD, Igielman F, Elwell C, Cope M, Smith M. Relationship of brain tissue PO2 to outcome after severe head injury. Crit Care Med. 1998;26(9):1576–81.

71. Kiening KL, Unterberg AW, BardTFT, Schneider GH, Lankisch WR. Monitoring of cerebral oxygenation in patients with severe head injuries: brain tissue PO2 versus jugular vein oxygen saturation. J Neurosurg. 1996;85(5):751–7.

72. Stiefel MF, Udoetek J, Spotta A, Gracias VH, Goldberg A, Maloney-Wilensky E, et al. Conventional neurocritical care does not ensure cerebral oxygenation after traumatic brain injury. J Neurosurg. 2006;105(4):568–75.

73. Timmons SD. Current trends in neurotrauma care. Crit Care Med. 2010;38(9 Suppl):S431–4.

74. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO2 to outcome after severe head injury. Crit Care Med. 1998;26(9):1576–81.

75. Meixensberger J, Jaeger M, Vath A, Dings J, Kunze E, Roosen K. Brain tissue oxygen guided treatment supplementing ICP/CPP therapy after traumatic brain injury. J Neurol Neurosurg Psychiatry. 2003;74(6):760–4.

76. Stiefel MF, Spotta A, Gracias VH, Garuffe AM, Guillaume MO, Maloney-Wilensky E, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. J Neurosurg. 2005;103(5):805–11.

77. Martini RP, Deen S, Yanez ND, Chestnut RM, Weiss NS, Daniel S, et al. Management guided by brain tissue oxygen monitoring and outcome following severe traumatic brain injury. J Neurosurg. 2009;111(4):644–9.

78. Diringer MN. Hyperoxia – good or bad for the injured brain? Curr Opin Crit Care. 2008;14(2):167–71.

79. Hlatky R, Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Brain tissue oxygen tension response to induced hyperoxia reduced in hyperperfused brain. J Neurosurg. 2008;108(1):53–8.

80. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, et al. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury. J Neurosurg. 2010;112(5):1080–94.

81. Smith M, Elwell C. Near-infrared spectroscopy: shedding light on the injured brain. Editorial. Anesth Analg. 2009;108(4):1055–7.

82. Thavosothy M, Broadhead M, Elwell C, Peters M, Smith M. A comparison of cerebral oxygenation as measured by the NIRO 300 and the INVOS 5100 near-infrared spectrophotometers. Anaesthesia. 2002;57(10):999–1006.

83. Al-Rawi PG, Kirkpatrick P. Tissue oxygen index: thresholds for cerebral ischaemia using near-infrared spectroscopy. Stroke. 2006;37(11):2720–5.

84. Kurth CD, McCann JC, Wu J, Miles L, Lootpe AW. Cerebral oxygen saturation-time threshold for hypoxic-ischaemic injury in piglets. Anesth Analg. 2009;108(4):1268–77.

85. Tisdall MM, Tachtsidis I, Leung TS, Elwell C, Smith M. Increase in cerebral aerobic metabolism by normobaric hyperoxia after traumatic brain injury. J Neurosurg. 2008;109(3):424–32.

86. Al-Rawi PG, Smielewski P, Kirkpatrick PJ. Evaluation of a near-infrared spectrometer (NIRO 300) for the detection of intracranial oxygenation changes in the adult head. Stroke. 2001;32(11):2492–500.

87. McGee AD, Igielman F, Elwell C, Cope M, Smith M. Measuring cerebral oxygenation during normobaric hyperoxia: a comparison of tissue microprobes, near-infrared spectroscopy, and jugular venous oximetry in head injury. Anesth Analg. 2003;97(3):851–6.
93. Peerdeman SM, Girbes AR, Polderman KH, Vandertop W. Changes in cerebral interstitial glycerol concentration in head-injured patients: correlation with clinical events. Intensive Care Med. 2003;29(10):1825–8.

94. Hillman J, Aneman O, Persson M, Andersson C, Dabrosin C, Mellergard P. Variations in the response of interleukins in neurosurgical intensive care patients monitored using intracerebral microdialysis. J Neurosurg. 2007;106(5):820–5.

95. Hlatky R, Goodman JC, Valadka AB, Robertson CS. Role of nitric oxide in cerebral blood flow abnormalities after traumatic brain injury. J Cereb Blood Flow Metab. 2003;23(5):582–8.

96. Marklund N, Blennow K, Zetterberg H, Ronne-Engstrom E, Enblad P, Hillerd L. Monitoring of brain interstitial total tau and beta amyloid proteins by microdialysis in patients with traumatic brain injury. J Neurosurg. 2009;110(6):1227–37.

97. Vespa PM, Nuwer MR, Nenov V, Ronne-Engstrom E, Hovda DA, Bergsneider M, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous EEG in the intensive care unit. J Neurosurg. 1999;91(5):750–60.

98. Vespa PM, Miller C, McArthur D, Eliseo M, Etchepare M, Hirt D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in delayed, prolonged increase in intracranial pressure and metabolic crisis. Crit Care Med. 2007;35(12):2830–6.

99. Vespa P, Prins M, Ronne-Engstrom E, Caron M, Shalmon E, Hovda DA, et al. Increase in extracellular glutamate caused by reduced cerebral perfusion pressure and seizures after human traumatic brain injury: a microdialysis study. J Neurosurg. 1998;89(6):971–82.

100. Hashemi P, Bhatia R, Nakamura H, Dreier JP, Graf R, Strong AJ, et al. Persisting depletion of brain glucose following cortical spreading depression, despite apparent hyperaemia: evidence for risk of an adverse effect of Leao’s spreading depression. J Cereb Blood Flow Metab. 2009;29(1):166–75.

101. Nortje J, Coles JP, Timofeev I, Fryer TD, Aigbirhio FI, Smielewski P, et al. Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: preliminary findings. Crit Care Med. 2008;36(1):273–81.

102. Reinsprug P, Stahl N, Mellergard P, Uski T, Ungerstedt U, Nordstorm CH. Intracerebral microdialysis in clinical practice: baseline values for chemical markers during wakefulness, anesthesia, and neurosurgery. Neurosurgery. 2000;47(3):701–9.

103. Schulz MK, Wang LP, Tange M, Bjerre P. Cerebral microdialysis monitoring: determination of normal and ischemic cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg. 2000;93(5):808–14.

104. Marion DW, Puccio A, Wisniewski SR, Kochanek P, Dixon CE, Bullian L, et al. Effect of hyperventilation on extracellular concentrations of glutamate, lactate, pyruvate, and local cerebral blood flow in patients with severe traumatic brain injury. Crit Care Med. 2002;30(12):2619–25.

105. Nordstrom C, Reinsprug P, Xu W, Gardenfors A, Ungerstedt U. Assessment of lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. Anesthesiology. 2003;98(4):809–14.