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Multimodal monitoring in traumatic brain injury: current status and future directions

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Traumatic brain injury (TBI) remains a major cause of morbidity and mortality, particularly in young people. Despite encouraging animal studies, human trials assessing the use of pharmacological agents after TBI have all failed to show efficacy. Current management strategies are therefore directed towards providing an optimal physiological environment in order to minimize secondary insults and maximize the body's own regenerative processes. Modern neurocritical care management utilizes a host of monitoring techniques to identify or predict the occurrence of secondary insults and guide subsequent therapeutic interventions in an attempt to minimize the resulting secondary injury. Recent data suggest that the use of protocolized management strategies, informed by multimodality monitoring, can improve patient outcome after TBI. Developments in multimodality monitoring have allowed a movement away from rigid physiological target setting towards an individually tailored, patient-specific, approach. The wealth of monitoring information available provides a challenge in terms of data integration and accessibility and modern software applications may aid this process.

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Pathophysiology of traumatic brain injury and the role of monitoring

The pathophysiology of TBI is usually described in terms of primary and secondary events and has been discussed in detail elsewhere in this issue. In summary, primary brain injury was originally defined as physical brain injury sustained at the moment of impact and secondary injury as injurious events, which occur at any later stage. Primary injuries were initially believed to be immediate and irreversible, but there is a growing body of evidence to suggest that a substantial component of cell death as a result of primary injury occurs hours after the injury and that its time-course overlaps with secondary, or additional, injury processes[44]. Secondary insults consist of a wide range of ischaemic, ionic, neurochemical, and immunological insults visited on a susceptible brain and the additional cerebral injury caused by these insults is known as secondary injury. The aetiology of secondary insults can be systemic, e.g. hypotension, hypoxaemia, anaemia, and acid–base or glucose disturbances, or intracranial, e.g. intracranial hypertension, cerebral oedema, seizures, regional cerebral blood flow (CBF) disturbance, metabolic and ionic derangement, excitotoxicity, free radical-induced damage, and mitochondrial dysfunction.[5 6 10 59] Secondary insults are common after TBI and have been reported to occur, at some point, in as many as 91% of patients requiring treatment in the neurointensive care unit.[30] Despite several encouraging animal studies, human TBI trials assessing pharmacological neuroprotective agents, such as glutamate antagonists, steroids, free radial scavengers, calcium channel antagonists, bradykinin antagonists, and growth factors, have all failed to show efficacy.[40] Current management strategies are therefore directed towards providing an optimal physiological environment in order to minimize secondary insults and maximize the body's own regenerative processes.

The goal of monitoring the injured brain is to enable the detection of harmful physiological events before they cause irreversible damage to the brain, thereby allowing diagnosis and effective treatment and providing 'on-line' feedback to guide therapy.[22] Through these interventions, the clinician aims to minimize secondary injury in an attempt to optimize patient management and outcome.[18 43] On the other hand, it has recently been suggested that monitoring and management of intracranial perfusion pressure (ICP) and cerebral perfusion pressure (CPP) after TBI may merely increase therapy intensity without improving outcome.[9]

Monitoring systemic physiological variables

As secondary insults to the injured brain can be either systemic or cerebral in origin, monitoring to detect these insults must have both systemic and cerebral components. Systemic variables routinely monitored during neurointensive care include electrocardiogram morphology, arterial oxygen saturation, arterial blood pressure (ABP), central venous pressure, cardiac output, systemic temperature, arterial blood gases, and serum electrolytes. These monitoring modalities will not be discussed further and this review will focus on invasive and non-invasive cerebral monitoring.

Invasive cerebral monitoring

Intracranial pressure

Measurement of ICP is central to the application of both ICP- and CPP-directed therapy, and ICP monitoring has become integral to the management of TBI in most units. Despite this, the use of ICP monitoring is not universal[4] and there exists no Class I evidence supporting its efficacy. Two main methods exist for the invasive measurement of ICP. The 'gold standard' technique is a catheter positioned with its tip in the lateral ventricle connected to a standard pressure transducer. This method measures global pressure and has the additional advantages of allowing periodic external calibration and therapeutic cerebrospinal fluid (CSF) drainage. However, placement of the ventricular catheter may be difficult in cases of severe brain swelling and there is a significant risk of developing ventriculitis with its attendant increased morbidity and mortality.[33] Transducer-tipped systems can be placed in the brain parenchyma or subdural space, either through a skull bolt on the neurointensive care unit (NICU) or by an open technique during a neurosurgical procedure with minimal infection and complication rates.[35] Measured pressure, however, may not be representative of true CSF pressure as transtentorial and interhemispheric pressure gradients may exist after TBI.[48] While these systems perform well during bench testing,[12] drift may occur during long-term monitoring and *in vivo* calibration is not possible. ICP monitoring allows measurement of absolute ICP concentrations, calculation of CPP and identification and analysis of pathological ICP waveforms. Cerebrovascular pressure reactivity and pressure–volume compensatory reserve may also be calculated.[14]

Oxygenation

Monitoring jugular venous oxygen saturation (Sv_{o_2}) is a technique, which can be used to estimate the balance between global cerebral oxygen delivery and utilization. A catheter is inserted into the dominant internal jugular vein (IJV) and advanced to the jugular bulb, thereby minimizing contamination from extracerebral venous return, which is around 3% if the catheter is correctly placed. Jugular Sv_{o_2} monitoring accurately reflects global cerebral oxygenation only if the dominant jugular bulb is cannulated[32] and the right side is often chosen because it is usually dominant.[47] However, the correct side can be identified more accurately by ultrasound examination of the IJV, by identifying the largest ICP increase caused by manual compression of each IJV or by identification of the larger jugular foramen on the computed tomography (CT) scan. Once catheter positioning has been checked on a lateral cervical spine radiograph, measurement of jugular Sv_{o_2} can be made either continuously using a fibre-optic catheter or directly by aspirating blood samples and using a co-oximeter. Reduction in jugular Sv_{o_2} below physiological levels ($<55\%$) indicates that cerebral oxygen delivery is inadequate to meet demand. In the context of TBI, this is most often related to reduced CBF secondary to decreased CPP or hyperventilation-associated vasoconstriction. Conversely, raised jugular Sv_{o_2} indicates luxury perfusion caused by either raised CBF or reduced oxygen demand secondary to mitochondrial dysfunction or cell death.[11] Reduction in jugular Sv_{o_2} to $<50\%$ after TBI is associated with poor outcome,[46] and jugular Sv_{o_2} is responsive to changes in CPP.[39] There is some evidence to suggest that the use of jugular Sv_{o_2} monitoring may improve outcome after TBI,[11] however jugular venous oximetry is limited by its lack of sensitivity to regional changes. It provides a flow-weighted average of cerebral Sv_{o_2} and has been shown to correlate poorly with regional tissue oxygenation in areas of focal pathology.[24] Furthermore, positron emission tomography (PET) evidence suggests that jugular Sv_{o_2} does not decrease by $<50\%$ until $\sim 13\%$ of the brain becomes ischaemic.[8] It is also possible that significant arteriovenous shunting, after TBI, might reduce the usefulness of this measurement.

Invasive probes have been developed to monitor focal tissue oxygen tension ($pBrO_2$). Currently, only one $pBrO_2$ monitor is commercially available for use in humans (Licox, GMS, Kiel-Mielkendorf, Germany). This $pBrO_2$ probe utilizes a closed polarographic (Clark-type) cell with reversible electrochemical electrodes. Oxygen, which has diffused from the brain tissue across a semi-permeable membrane, is reduced by a gold polarographic cathode and produces a flow of electrical current directly proportional to the oxygen concentration and related to the brain temperature.[42] Measured $pBrO_2$ represents the balance between oxygen delivery and cellular oxygen consumption, but is also affected by changes in diffusion distance from capillary to probe and the proportion of arterioles and venules in the region of interest. It remains a matter of debate whether measured $pBrO_2$ more closely relates to CBF or oxygen extraction fraction.[50] $pBrO_2$ probes provide a highly focal measurement and while this offers the potential of selectively monitoring critically perfused tissue, it means that probe positioning is crucial and

that global changes may be missed. Normal $pBrO_2$ values are in the region of 35–50 mm Hg.[25 38]

After TBI, $pBrO_2$ increases with CPP and the ceiling of this effect is higher in the areas of focal ischaemia.[56] Comparative studies have also shown correlation between $pBrO_2$ and regional CBF,[50] and between changes in $pBrO_2$ and changes in regional Sv_{O_2} measured using PET.[23] Although it has been demonstrated that reduced $pBrO_2$ is associated with poor outcome after TBI, the threshold for hypoxia has proved more difficult to identify and is likely to be related to both the duration and level of hypoxia. Ischaemic thresholds of between 5 and 20 mm Hg have been suggested.[60 62] It is clear that $pBrO_2$ can be altered using clinical intervention, and that measured levels relate to outcome. What is less clear is whether the manipulation of this variable can affect outcome. Recent evidence, however, suggests that $pBrO_2$-directed therapy may improve outcome and this possibility merits further investigation.[55]

Cerebral microdialysis

Cerebral microdialysis (MD) is a well-established laboratory tool and is being increasingly used as a bedside monitor to provide on-line analysis of brain tissue biochemistry during neurointensive care. Cerebral MD has recently been reviewed in depth.[58] Placement of the MD catheter in 'at-risk' tissue, such as the area surrounding a mass lesion after TBI allows biochemical changes to be measured in the area of brain most vulnerable to secondary insult (Fig. 1). Commercial assays are available to measure dialysate concentrations of glucose, lactate, pyruvate, glycerol and glutamate, and tentative normal values for these variables have been described.[45]

In the human brain, severe hypoxia/ischaemia is typically associated with marked increases in the lactate: pyruvate ratio (LPR),[54] which correlates with the PET-measured oxygen extraction fraction.[27] An increase in LPR above established thresholds (20–25) is associated with poor outcome in TBI,[68] and has traditionally been assumed to indicate tissue ischaemia. However, it has proved difficult to establish the hypoxic threshold associated with raised LPR[29] and it is increasingly apparent that anaerobic glycolysis may occur as a result of the failure of effective utilization of delivered oxygen because of mitochondrial failure and hypoxia/ischaemia.[64] Failure of cellular metabolism eventually leads to degradation of cell membrane phospholipids and release of glycerol into the brain extracellular fluid (ECF). Glycerol is therefore a useful MD marker of cell damage after TBI[7] and the degree of the hypoxia/ischaemia-induced elevation of MD glycerol may be dramatic, with 4- or 8-fold increases recorded in severe or complete ischaemia, respectively.[51] Cerebral MD glycerol concentrations are typically elevated in the first 24 h after severe TBI, presumably as a result of the primary injury, and then exponentially decline during the ensuing 3 days.[7] Subsequent increases in MD glycerol concentration are associated with adverse secondary events[45] and seizure activity.[63] Increased concentrations of excitatory amino acids[31] and reduced brain ECF glucose concentrations[66] may also predict or be associated with metabolic catastrophes occurring after acute brain injury. MD is becoming established as a tool to assist clinical decision-making during neurointensive care, such as management of CPP,[41] guidance of hyperventilation,[34] and the appropriateness of extensive surgical procedures.[3]

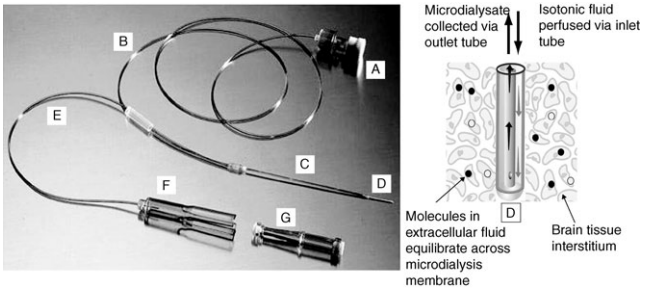

Fig 1 Components of clinical MD catheter and schematic representation of an MD catheter in brain tissue. A, Pump connector; B, inlet tube; C, MD catheter; D, MD membrane; E, outlet tube; F, microvial holder; G, microvial for collection of microdialysate (adapted from Tisdall and Smith[58]).

Cerebrovascular autoregulation

Cerebrovascular autoregulation is frequently impaired after TBI and is associated with poor outcome.[17] Continuous monitoring of cerebral autoregulation may predict patients at risk of secondary injury and may help to define individual treatment targets. Several techniques have been developed for monitoring indices of autoregulation and those relating to ICP[16] and $pBrO_2$[28] show prognostic ability. These techniques calculate a continuous correlation between ABP and either ICP or $pBrO_2$, and thus assess the cerebral response to spontaneous fluctuations in ABP.

Non-invasive cerebral monitoring

Cerebral imaging

Cerebral imaging techniques can provide detailed haemodynamic and metabolic information over multiple regions of interest and have been reviewed elsewhere in this issue. In terms of clinical management of patients, they are all limited by two serious disadvantages. First, they are only able to provide snapshot images of the brain and therefore cannot be used to track the course of brain injury over time or guide neuroprotective treatment strategies in real-time. Second, they require the transfer of critically ill patients to specialized imaging facilities and prolonged scanning time,

both of which can be detrimental to the patient's condition. Only bedside techniques are considered in this review.

Transcranial Doppler ultrasonography

Transcranial Doppler (TCD) is a non-invasive technique, which uses ultrasound waves to derive CBF velocity from the Doppler shift caused by red-blood cells moving through the field of view. A low-frequency (2 MHz) pulsed wave probe is used to insonate a basal cerebral vessel through an acoustic cranial window, an area of the skull with sparse, or no cancellous bone that causes little attenuation and scattering of the signal. The TCD flow velocity waveform resembles an arterial pulse wave and may be quantified into peak systolic, end diastolic and mean flow velocities. TCD is not able to provide absolute measurements of CBF but, if the angle of insonation and the diameter of the insonated vessel remain constant, changes in TCD-measured CBF velocity will reflect changes in CBF.[61] TCD has also been used to test autoregulatory reserve by monitoring changes in CBF velocity in response to changes in mean arterial pressure, and this technique may have a role in providing individual-specific CPP targets.[15] TCD is also widely used to diagnose and monitor cerebral vasospasm after subarachnoid haemorrhage[52] and has also been used to estimate ICP non-invasively.[13]

Continuous electroencephalography

Seizures are a source of secondary insult to the injured brain, tend to occur in the first few days after TBI and are associated with higher injury severity and worse outcome. Recent data from continuous electroencephalography (cEEG) studies demonstrate that seizures occur in ~20% of patients with TBI on the NICU.[67] Many of these seizures are of the non-convulsive variety and cannot be detected clinically and some occur despite the use of prophylactic phenytoin at adequate serum concentrations. cEEG generates large quantities of data and systems must be developed, which are able to reduce the data volume and flag up potential abnormalities.[49] One methodology, which has shown potential, is the use of alpha variability in cEEG recordings to predict outcome after TBI.[65]

Near infrared spectroscopy

Near infrared spectroscopy (NIRS) is a non-invasive technique based on the transmission and absorption of near infrared light (700–1000 nm) as it passes through tissue. Oxygenated and deoxygenated haemoglobin have different absorption spectra and cerebral oxygenation and haemodynamic status can be determined by their relative absorption of near infrared light. Earlier methodology was limited to measuring changes in concentrations of these tissue chromophores,[36] but recent advances have allowed measurement of absolute haemoglobin oxygen saturation[57] and absolute concentrations of oxy- and deoxy-haemoglobin.[19] Techniques have been described for the calculation of regional CBF[20] and cerebral blood volume,[26] but are not well validated. It is also possible to measure changes in the concentration of the terminal complex of the electron transfer chain, cytochrome *c* oxidase. This measurement has been validated in animal studies as a measure of changes in cellular energy status and offers the potential to assess intramitochondrial redox and the adequacy of oxygen delivery.[53] NIRS has the potential to provide continuous non-invasive measurement of cerebral haemodynamic and metabolic parameters over multiple regions of interest with high temporal resolution. Spatially resolved spectroscopy has high sensitivity and specificity to intracranial changes[2] and has been compared with jugular venous oximetry and brain oxygen tension in patients with TBI.[37] Tentative ischaemic thresholds for NIRS variables have recently been described,[1] but clinical data on the application of NIRS after TBI are limited. Issues also remain concerning the influence of extracranial tissues and the distribution of the transmitted light and NIRS currently remains a research technique on the NICU.

Recent developments

The last decade has seen increases in the quantity of cerebral monitoring data available to the clinician and a patient being treated for TBI in the modern NICU is surrounded by monitoring and medical devices (Fig. 2). This trend is set to continue, driven by further technological advances. The miniaturization of devices continues at an unprecedented rate and this paves the way for development of implantable and diagnostic devices. On a larger scale mobile CT and single photon emission computed tomography imaging equipment, which can be used at the bedside on the NICU, is now available. The search for biomarkers of secondary cerebral injury continues and cerebral MD may have an important role to play in this process as it offers great flexibility in the range of metabolites that can be sampled.

The real challenge however may be the development of systems that are able to integrate this vast array of data and present them to the clinician in a digestible format and suitable systems are being developed.[21] 'Intelligent' software is required in order to identify trends and associations between the monitored variables and highlight patients at risk of deterioration at an early stage. Complex analysis of monitoring data sets might also identify monitoring modalities which are most efficacious for prognostication and treatment target setting and therefore aid the establishment of core monitoring requirements.

Conclusion

Many of the cerebral monitoring techniques currently available have drawbacks when considered in isolation. Invasive hyperfocal techniques provide continuous information relating to a single region of the brain, and carry an

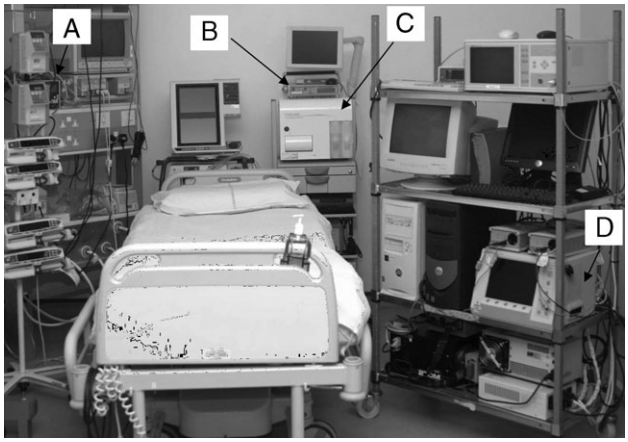

Fig 2 Devices used for monitoring patients with TBI in the modern NICU. A, Intracranial pressure monitor; B, brain oxygen tension monitor; C, microdialysis analyser; D, near infrared spectrometer.

attendant risk of complications, whereas non-invasive imaging techniques provide high spatial resolution at multiple sites, but with greatly reduced temporal resolution and necessitate the transfer of critically ill patients to remote sites. cEEG and NIRS can provide multisite measurements with high temporal resolution, but at the cost of reduced spatial resolution. The challenge therefore is to integrate monitoring systems in order to combine their strengths, improve artifact rejection, and allow greater confidence in decision-making. Modern multimodality monitoring systems provide the clinician with a diverse range of data, but techniques are required to assist in the analysis and integration of these data. Multimodality monitoring may allow greater understanding of individual pathophysiology and allow delivery of tailored treatment strategies rather than strict adherence to universal physiological targets. Individualized treatment informed by multimodality monitoring has the potential to improve patient outcome after TBI.

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References

1 Al-Rawi PG, Kirkpatrick PJ. Tissue oxygen index: thresholds for cerebral ischemia using near-infrared spectroscopy. *Stroke* 2006; **37**: 2720–5

2 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**: 2492–500

3 Boret H, Fesselet J, Meaudre E, Gaillard PE, Cantais E. Cerebral microdialysis and $PtiO_2$ for neuro-monitoring before decompressive craniectomy. *Acta Anaesthesiol Scand* 2006; **50**: 252–4

4 Bulger EM, Nathens AB, Rivara FP, *et al*. Management of severe head injury: institutional variations in care and effect on outcome. *Crit Care Med* 2002; **30**: 1870–6

5 Chesnut RM. Secondary brain insults after head injury: clinical perspectives. *New Horiz* 1995; **3**: 366–75

6 Choi DW. Ionic dependence of glutamate neurotoxicity. *J Neurosci* 1987; **7**: 369–79

7 Clausen T, Alves OL, Reinert M, Doppenberg E, Zauner A, Bullock R. Association between elevated tissue glycerol levels and poor outcome following severe traumatic brain injury. *J Neurosurg* 2005; **103**: 233–8

8 Coles JP, Fryer TD, Smielewski P, *et al*. Incidence and mechanisms of cerebral ischemia in early clinical head injury. *J Cereb Blood Flow Metab* 2004; **24**: 202–11

9 Cremer OL, van Dijk GW, van Wensen E, *et al*. Effect of intracranial pressure monitoring and targeted intensive care on functional outcome after severe head injury. *Crit Care Med* 2005; **33**: 2207–13

10 Crompton M. The mitochondrial permeability transition pore and its role in cell death. *Biochem J* 1999; **341**: 233–49

11 Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobin saturation: management strategies and clinical outcome. *Crit Care Med* 1998; **26**: 344–51

12 Czosnyka M, Czosnyka Z, Pickard JD. Laboratory testing of three intracranial pressure microtransducers: technical report. *Neurosurgery* 1996; **38**: 219–24

13 Czosnyka M, Matta B, Smielewski P, *et al*. Cerebral perfusion pressure in head-injured patients: a noninvasive assessment using transcranial Doppler ultrasonography. *J Neurosurg* 1998; **88**: 802–8

14 Czosnyka M, Pickard JD. Monitoring and interpretation of intracranial pressure. *J Neurol Neurosurg Psychiatry* 2004; **75**: 813–21

15 Czosnyka M, Smielewski P, Czosnyka Z, *et al*. Continuous assessment of cerebral autoregulation: clinical and laboratory experience. *Acta Neurochir Suppl* 2003; **86**: 581–5

16 Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. *Neurosurgery* 1997; **41**: 11–7

17 Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD. Cerebral autoregulation following head injury. *J Neurosurg* 2001; **95**: 756–63

18 Fakhry SM, Trask AL, Waller MA, Watts DD. Management of brain-injured patients by an evidence-based medicine protocol improves outcomes and decreases hospital charges. *J Trauma* 2004; **56**: 492–9

19 Fantini S, Hueber D, Franceschini MA, *et al*. Non-invasive optical monitoring of the newborn piglet brain using continuous-wave and frequency-domain spectroscopy. *Phys Med Biol* 1999; **44**: 1543–63

20 Gora F, Shinde S, Elwell CE, *et al*. Noninvasive measurement of cerebral blood flow in adults using near-infrared spectroscopy and indocyanine green: a pilot study. *J Neurosurg Anesthesiol* 2002; **14**: 218–22

21 Guendling K, Smielewski P, Czosnyka M, *et al*. Use of ICM+ software for on-line analysis of intracranial and arterial pressures in head-injured patients. *Acta Neurochir Suppl* 2006; **96**: 108–13

22 Gupta AK. Application of multimodal monitoring. In: Gupta AK and Summors A, eds. *Notes in Neuroanaesthesia and Critical Care*. London: Greenwich Medical Media, 2001: 260–2

23 Gupta AK, Hutchinson PJ, Fryer T, *et al*. Measurement of brain tissue oxygenation performed using positron emission tomography scanning to validate a novel monitoring method. *J Neurosurg* 2002; **96**: 263–8

24 Gupta AK, Hutchinson PJ, Al-Rawi P, *et al*. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. *Anesth Analg* 1999; **88**: 549–53

25 Hoffman WE, Charbel FT, Edelman G. Brain tissue oxygen, carbon dioxide, and pH in neurosurgical patients at risk for ischemia. *Anesth Analg* 1996; **82**: 582–6

26 Hopton P, Walsh TS, Lee A. Measurement of cerebral blood volume using near-infrared spectroscopy and indocyanine green elimination. *J Appl Physiol* 1999; **87**: 1981–7

27 Hutchinson PJ, Gupta AK, Fryer TF, *et al*. Correlation between cerebral blood flow, substrate delivery, and metabolism in head injury: a combined microdialysis and triple oxygen positron emission tomography study. *J Cereb Blood Flow Metab* 2002; **22**: 735–45

28 Jaeger M, Schuhmann MU, Soehle M, Meixensberger J. Continuous assessment of cerebrovascular autoregulation after traumatic brain injury using brain tissue oxygen pressure reactivity. *Crit Care Med* 2006; **34**: 1783–8

29 Johnston AJ, Steiner LA, Coles JP, *et al*. Effect of cerebral perfusion pressure augmentation on regional oxygenation and metabolism after head injury. *Crit Care Med* 2005; **33**: 189–95

30 Jones PA, Andrews PJ, Midgley S, *et al*. Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesth* 1994; **6**: 4–14

31 Kett-White R, Hutchinson PJ, Al-Rawi PG, Gupta AK, Pickard JD, Kirkpatrick PJ. Adverse cerebral events detected after subarachnoid hemorrhage using brain oxygen and microdialysis probes. *Neurosurgery* 2002; **50**: 1213–21

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

33 Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES, Jr. Ventriculostomy-related infections: a critical review of the literature. *Neurosurgery* 2002; **51**: 170–81

34 Marion DW, Puccio A, Wisniewski SR, *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**: 2619–25

35 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**: 82–6

36 Matcher SJ, Elwell CE, Cooper CE, Cope M, Delpy DT. Performance comparison of several published tissue near-infrared spectroscopy algorithms. *Anal Biochem* 1995; **227**: 54–68

37 McLeod 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**: 851–6

38 Meixensberger J, Dings J, Kuhnigk H, Roosen K. Studies of tissue pO2 in normal and pathological human brain cortex. *Acta Neurochir Suppl (Wien)* 1993; **59**: 58–63

39 Murr R, Schurer L. Correlation of jugular venous oxygen saturation to spontaneous fluctuations of cerebral perfusion pressure in patients with severe head injury. *Neurol Res* 1995; **17**: 329–33

40 Narayan RK, Michel ME, Ansell B, *et al*. Clinical trials in head injury. *J Neurotrauma* 2002; **19**: 503–57

41 Nordstrom C, Reinstrup 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**: 809–14

42 Nortje J, Gupta AK. The role of tissue oxygen monitoring in patients with acute brain injury. *Br J Anaesth* 2006; **97**: 95–106

43 Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ, Kirkpatrick PJ. Specialist neurocritical care and outcome from head injury. *Intensive Care Med* 2002; **28**: 547–53

44 Reilly PL. Brain injury: the pathophysiology of the first hours. Talk and die revisited. *J Clin Neurosci* 2001; **8**: 398–403

45 Reinstrup P, Stahl N, Mellergard P, Uski T, Ungerstedt U, Nordstrom CH. Intracerebral microdialysis in clinical practice: baseline values for chemical markers during wakefulness, anesthesia, and neurosurgery. *Neurosurgery* 2000; **47**: 701–9

46 Robertson CS, Gopinath SP, Goodman JC, Contant CF, Valadka AB, Narayan RK. $SjvO_2$ monitoring in head-injured patients. *J Neurotrauma* 1995; **12**: 891–6

47 Robertson CS, Narayan RK, Gokaslan ZL, *et al*. Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *J Neurosurg* 1989; **70**: 222–30

48 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**: 16–26

49 Scheuer MJ. Continuous EEG monitoring in the intensive care unit. *Epilepsia* 2002; **43**: 114–27

50 Scheufler KM, Rohrborn HJ, Zentner J. Does tissue oxygen-tension reliably reflect cerebral oxygen delivery and consumption? *Anesth Analg* 2002; **95**: 1042–8

51 Schulz M, Wang L, Tange M, Bjerre P. Cerebral microdialysis monitoring: determination of normal and ischemic cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2000; **93**: 233–8

52 Springborg JB, Frederiksen HJ, Eskesen V, Olsen NV. Trends in monitoring patients with aneurysmal subarachnoid haemorrhage. *Br J Anaesth* 2005; **94**: 259–70

53 Springett RJ, Wylezinska M, Cady EB, Hollis V, Cope M, Delpy DT. The oxygen dependency of cerebral oxidative metabolism in the newborn piglet studied with 31P NMRS and NIRS. *Adv Exp Med Biol* 2003; **530**: 555–63

54 Stahl N, Mellergard P, Hallstrom A, Ungerstedt U, Nordstrom CH. Intracerebral microdialysis and bedside biochemical analysis in patients with fatal traumatic brain lesions. *Acta Anaesthesiol Scand* 2001; **45**: 977–85

55 Stiefel MF, Spiotta A, Gracias VH, *et al*. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg* 2005; **103**: 805–11

56 Stocchetti N, Chieregato A, De Marchi M, Croci M, Benti R, Grimoldi N. High cerebral perfusion pressure improves low values of local brain tissue O_2 tension ($PtiO_2$) in focal lesions. *Acta Neurochir Suppl* 1998; **71**: 162–5

57 Suzuki S, Takasaki S, Ozaki T, Kobayashi Y. A tissue oxygenation monitor using NIR spatially resolved spectroscopy. *SPIE Proc* 1999; **3597**: 582–92

58 Tisdall MM, Smith M. Cerebral microdialysis: research technique or clinical tool. *Br J Anaesth* 2006; **97**: 18–25

59 Unterberg AW, Stover JF, Kress B, Kiening KL. Edema and brain trauma. *Neuroscience* 2004; **129**: 1021–9

60 Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO_2 to outcome after severe head injury. *Crit Care Med* 1998; **26**: 1576–81

61 Valdueza JM, Balzer JO, Villringer A, Vogl TJ, Kutter R, Einhaupl KM. Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. *Am J Neuroradiol* 1997; **18**: 1929–34

62 van Santbrink H, Maas AI, Avezaat CJ. Continuous monitoring of partial pressure of brain tissue oxygen in patients with severe head injury. *Neurosurgery* 1996; **38**: 21–31

63 Vespa P, Martin NA, Nenov V, *et al*. Delayed increase in extracellular glycerol with post-traumatic electrographic epileptic activity: support for the theory that seizures induce secondary injury. *Acta Neurochir Suppl* 2002; **81**: 355–57

64 Vespa P, Bergsneider M, Hattori N, *et al*. Metabolic crisis without brain ischemia is common after traumatic brain injury: a combined microdialysis and positron emission tomography study. *J Cereb Blood Flow Metab* 2005; **25**: 763–74

65 Vespa PM, Boscardin WJ, Hovda DA, *et al*. Early and persistent impaired percent alpha variability on continuous electroencephalography monitoring as predictive of poor outcome after traumatic brain injury. *J Neurosurg* 2002; **97**: 84–92

66 Vespa PM, McArthur D, O'Phelan K, *et al*. Persistently low extracellular glucose correlates with poor outcome 6 months after human traumatic brain injury despite a lack of increased lactate: a microdialysis study. *J Cereb Blood Flow Metab* 2003; **23**: 865–77

67 Vespa PM, Nuwer MR, Nenov V, *et al*. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *J Neurosurg* 1999; **91**: 750–60

68 Zauner A, Doppenberg E, Woodward JJ, Choi SC, Young HF, Bullock R. Continuous monitoring of cerebral substrate delivery and clearance: initial experience in 24 patients with severe acute brain injuries. *Neurosurgery* 1997; **41**: 1082–91