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Multimodality Neuromonitoring in Adult Traumatic Brain Injury

A Narrative Review

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ABSTRACT

Neuromonitoring plays an important role in the management of traumatic brain injury. Simultaneous assessment of cerebral hemodynamics, oxygenation, and metabolism allows an individualized approach to patient management in which therapeutic interventions intended to prevent or minimize secondary brain injury are guided by monitored changes in physiologic variables rather than generic thresholds. This narrative review describes various neuromonitoring techniques that can be used to guide the management of patients with traumatic brain injury and examines the latest evidence and expert consensus guidelines for neuromonitoring. **(Anesthesiology 2018; 128:401-15)**

TRAUMATIC brain injury (TBI) is a leading cause of death and disability worldwide. Clinical outcomes are determined not only by the severity of the initial injury but also by biochemical, excitotoxic, and inflammatory responses that lead to further (secondary) brain injury.[1] The management of TBI is based on the central concept that prevention of secondary brain injury is associated with improved outcomes. Neuromonitoring plays an important role in the management of TBI because it is able to assess multiple aspects of cerebral physiology and guide therapeutic interventions intended to prevent or minimize secondary injury.[2–4] No single neuromonitor is able to identify comprehensively the spectrum of pathophysiologic changes after TBI, and multimodality monitoring—the measurement of several variables simultaneously—provides a more comprehensive picture of the (patho)physiology of the injured brain and its response to treatment.[5] Assessment of cerebral hemodynamics, oxygenation, and metabolic status allow an individually tailored approach to patient management in which treatment decisions can be guided by monitored changes in physiologic variables rather than by predefined, generic thresholds.[4] Several monitoring techniques are available for clinical use (table 1). Normal ranges and treatment thresholds for many monitored variables are derived from observational data studying a variety of correlates of tissue injury rather than clinical outcomes. Furthermore, there is uncertainty about which physiologic variables are the most clinically relevant, how and when they should be monitored, and whether monitoring is cost-effective and impacts outcome.[2] Expert consensus guidelines on multimodality neuromonitoring have been published by the Neurocritical Care Society and the European Society of Intensive Care Medicine after comprehensive review of the literature.[6]

Clinical Monitoring

Clinical assessment using objective scales to assess consciousness and motor power is a key component of neuromonitoring.[7] The Glasgow coma scale was the first attempt to standardize assessment of neurologic state after TBI by recording best eye opening and verbal and motor responses to standardized verbal and physical stimuli.[8] The Glasgow coma score is used to classify the severity of TBI, identify changes in neurologic state by means of serial recording, and assist in prognostication, although it does have some limitations. Verbal responses cannot be assessed in intubated patients, brainstem function is not tested, and a Glasgow coma score of 3 may cover a spectrum of brain injury severity. Alternative clinical assessment methods such as the Full Outline of UnResponsiveness (FOUR) score that assesses four components of neurologic function—eye, motor, brainstem, and respiratory functions—have been developed to overcome some of these limitations.[9] However, newer scoring systems have not been widely adopted, and the

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Table 1. Multimodal Neuromonitoring in Traumatic Brain Injury

Technique	Advantages	Disadvantages	Thresholds for Intervention
Intracranial pressure			
Ventricular catheter	• Measures global pressure • Therapeutic drainage of cerebrospinal fluid to manage ICP • *In vivo* calibration	•Placement technically difficult • Risk of hemorrhage • Risk of infection	ICP > 22 mmHg
Microsensor	• Intraparenchymal/subdural placement • Low procedural complication rate • Low infection risk	• *In vivo* calibration not possible • Measures localized pressure	ICP > 22 mmHg
Noninvasive methods	• Low risk • Use in coagulopathic patients	• Insufficiently accurate for routine clinical use • Many unable to offer continuous monitoring	
Cerebral oxygenation			
Jugular venous oximetry	• Straightforward to perform • Easy to interpret • Real time and continuous • Global trend monitor	• Insensitive to regional ischemia • Requires correct catheter placement to avoid contamination from extracranial circulation • Invasive procedure; risk of hematoma, carotid puncture, and vein thrombosis	Jugular venous oxygen saturation ≤ 50–55%
Brain tissue P_{O_2}	• Gold standard for bedside cerebral oxygenation monitoring • Real time and continuous • Focal monitor of critically perfused tissue • Low complication rate – hematoma risk < 2%, no reported infections	• Invasive • Utility dependent on probe location; at-risk but viable tissue; regional monitor; normal-appearing frontal lobe; global measure • 1-h run-in period required	Brain tissue P_{O_2} ≤ 15–20 mmHg
Near infrared spectroscopy	• Noninvasive assessment of regional cerebral tissue oxygenation • High spatial and temporal resolution • Assessment over multiple regions of interest simultaneously	• Lack of standardization between commercial devices • Ischemic thresholds not defined • Signals affected by extracerebral tissue • Not recommended for routine clinical use	Not determined
Cerebral autoregulation	• Identification of optimal CPP range • Interpretation of relationships between cerebral blood flow, oxygen delivery/demand, and cellular metabolism	• Requires high-frequency signal processing • Insufficient data to support recommendation for routine clinical use	N/A
Cerebral blood flow			
Transcranial Doppler	• Noninvasive • Real-time, continuous monitoring	• Relative rather than absolute cerebral blood flow • Operator dependent • Failure rate in up to 10% of patients; absent acoustic window	Increased blood flow velocity and pulsatility index
Thermal diffusion flowmetry	• Continuous measurement of absolute regional cerebral blood flow	• Concerns over reliability • Limited clinical data	Not determined
Cerebral microdialysis	• Measurement of brain tissue biochemistry • Early detection of hypoxia/ischemia • Monitor of ischemic and nonischemic causes of cellular bioenergetic distress	• Focal measure • Thresholds for intervention uncertain	Glucose < 0.7 mM Lactate:pyruvate ratio > 25–40 Lactate > 4.0 mM

(*Continued*)

Table 1. (Continued)

Technique	Advantages	Disadvantages	Thresholds for Intervention
Electroencephalography			
Scalp EEG	• Noninvasive • Correlates with ischemic and metabolic changes • Assessment of nonconvulsive seizures/status epilepticus	• Skilled interpretation required • Affected by anesthetic/sedative agents • Misses some seizure activity • Cannot identify cortical spreading depolarizations	N/A
Invasive EEG (subdural strip/depth electrodes)	• Identifies abnormalities missed by scalp EEG monitoring • Only method to monitor cortical spreading depolarizations	• Invasive • Labor intensive	N/A

CPP = cerebral perfusion pressure; EEG = electroencephalography; ICP = intracranial pressure; N/A = not applicable.

Glasgow coma score remains the most popular clinical assessment scale of neurologic status more than 40 yr since its first description. In addition to assessment of consciousness, it is also important to identify and document focal limb deficits using the validated Medical Research Council scale and pupil responses.[10] Infrared pupillometry provides an objective assessment of pupillary reactivity and may be superior to its clinical assessment.[11]

Deep sedation and the use of muscle relaxants prevent informative clinical assessment, and sedation holds to allow neurologic examination are not recommended in patients with raised intracranial pressure (ICP).[10] Furthermore, clinical examination may not reliably detect subtle changes in intracranial physiology, and alterations in neurologic state can occasionally occur late. Clinical assessment should therefore be seen as a compliment to neuromonitoring and *vice versa*.

Intracranial Pressure and Derived Indices

The monitoring and management of ICP is the cornerstone of neuromonitoring after TBI, although the indications for monitoring continue to generate debate. In addition to absolute ICP measurement, ICP monitoring allows calculation of cerebral perfusion pressure (CPP) and waveform analysis assessment of cerebrovascular reactivity and autoregulatory status.[12]

Intracranial Pressure

Two methods of monitoring ICP are commonly used in clinical practice: ventricular catheters and microtransducer devices (strain gauge or fiberoptic types).[13] Ventricular catheters measure global ICP and have the advantage of allowing therapeutic drainage of cerebrospinal fluid to treat intracranial hypertension. However, they are associated with higher complication rates, including infection, compared to microtransducer systems. The latter are sited in brain parenchyma or subdural space and measure localized ICP, although this correlates with ventricular pressure in most circumstances.[14] Several noninvasive ICP monitoring techniques have been described including transcranial Doppler flow velocity waveform morphology or derived pulsatility index[15] and ultrasound or computed tomography measurement of optic nerve sheath diameter.[16] However, many noninvasive techniques are unable to monitor intracranial dynamics continuously, and most are insufficiently accurate for routine clinical use.[17]

Despite absence of high-quality evidence, the fourth edition of the Brain Trauma Foundation guidelines (2016) recommends ICP monitoring in all salvageable patients with severe TBI and an abnormal computed tomography scan (presence of hematomas, contusions, swelling, herniation, or compressed basal cisterns) and also in those with a normal scan and two of three high-risk characteristics (age more than 40 yr, motor posturing, and systolic blood pressure less than 90 mmHg).[18] Alternative guidelines (the Milan consensus) from a group of mainly European clinical experts provide pragmatic and specific recommendations for ICP monitoring for different TBI scenarios and cranial computed tomography findings.[19] Although there is much consistency between the two, in contrast to those from the Brain Trauma Foundation, the Milan consensus statement does not recommend routine ICP monitoring in comatose TBI patients with a normal computed tomography scan but advises a second scan and institution of monitoring only if there is radiologic worsening (table 2). All clinical guidelines advocate early treatment of raised ICP after TBI, although recommended treatment thresholds may vary. The Brain Trauma Foundation recommends treatment of ICP of greater than or equal to 22 mmHg based on evidence that ICP–guided management of severe TBI may reduce in-hospital and 2-week postinjury mortality.[18]

Raised ICP is a long-established and important cause of TBI-related secondary brain injury and has been associated with higher mortality and poor long-term functional outcomes in many studies.[20,21] In contrast, a secondary analysis of data from a randomized trial of severe TBI found that average ICP was not independently associated with worse neuropsychologic function in survivors at 6 months after injury.[22] It is the overall burden (or "dose") of intracranial

Table 2. Indications for Intracranial Pressure Monitoring in Traumatic Brain Injury

Brain Trauma Foundation guidelines (2016)
- Salvageable patients with severe TBI and abnormal cranial CT scan (intracranial hematomas, contusions, swelling, herniation, or compressed basal cisterns)
- Salvageable patients with severe TBI and normal scan with two or more of the following risk factors:
  - Age > 40 yr
  - Motor posturing (unilateral or bilateral)
  - Systolic blood pressure < 90 mmHg

Milan consensus conference (2014)
- ICP monitoring is generally not recommended in comatose TBI patients with a normal initial CT findings
  - Routine second CT scan recommended because of potential for radiologic worsening
  - Urgent CT scan if clinical deterioration
- ICP monitoring should be undertaken in comatose TBI patients with
  - Worsening CT findings (even if initial CT scan showing minimal signs of injury)
  - Cerebral contusions when interruption of sedation to monitor neurologic status is contraindicated or when clinical examination is unreliable
  - Large bi-frontal contusions and/or hemorrhagic mass lesions close to the brainstem irrespective of initial GCS
- ICP monitoring should also be undertaken
  - After evacuation of an acute supratentorial intracranial hematoma in salvageable patients at increased risk of intracranial hypertension, including those with:
  - Glasgow coma scale motor score ≤ 5
  - Pupillary abnormalities
  - Prolonged hypoxia and/or hypotension
  - Compressed or obliterated basal cisterns
  - Midline shift > 5 mm
  - Additional extraaxial hematoma, parenchymal contusions, cerebral edema
  - Intraoperative brain swelling
  - After secondary decompressive craniectomy to monitor effectiveness of ICP control and guide ongoing management
  - In polytrauma patients requiring multiple procedures under general anesthesia or prolonged sedation

CT = computed tomography; GCS = Glasgow coma score; ICP = intracranial pressure; TBI = traumatic brain injury.

hypertension—its duration as well as severity—that is the prognostic factor,[23,24] particularly if elevated ICP is refractory to treatment.[25] Despite evidence of potential mortality benefits from ICP monitoring–guided therapy, several studies report monitoring rates less than 50% in patients eligible for monitoring according to standard guidelines.[26–28] In a multicenter study, ICP monitoring was associated with an 8.3-percentage point reduction in risk-adjusted mortality rate but undertaken in only 46% of 844 eligible patients.[26] On the other hand, a single-center study found that patients eligible for ICP monitoring who did not have a monitor placed were 1.21 times more likely to survive compared to those who underwent monitoring.[29] The largest, multicenter observational study of ICP monitoring to date confirmed that monitoring is associated with lower in-hospital mortality after TBI, although the observed interinstitution variability in ICP monitoring rates in this study contributed only modestly to the substantial variability in mortality.[30] This emphasizes that it is the impact of monitor-guided therapeutic interventions, rather than monitoring *per se*, that are the critical determinants of outcome.

Based on historic, observational data, the thresholds for initiation and escalation of treatment of intracranial hypertension have traditionally been set at between 20 and 25 mmHg,[31] despite reports that lower and higher ICP thresholds are associated with poor outcome[20] and in the absence of direct evidence of benefit from this approach.[32] The only randomized clinical trial evaluating the utility of ICP monitoring in TBI—the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST:TRIP) trial—found similar 3- and 6-month outcomes in patients in whom treatment was guided by ICP monitoring compared to treatment guided by imaging and clinical examination in the absence of ICP monitoring.[33] Because both treatment approaches provided satisfactory outcomes despite the absence of ICP monitoring in one, the results of this study challenge the established practice of maintaining ICP below universal and arbitrary thresholds.[34] Reliance on absolute ICP thresholds as recommended by some clinical guidelines ignores the variability of brain injury after TBI, different host characteristics and responses, and temporal changes in pathophysiology. It is now recognized that treatment interventions can be better optimized by individualized interpretation of ICP values in association with other neuromonitoring variables (described in subsequent sections), patient characteristics, and after assessment of the potential benefits and risks of treatment.[35]

The possibility of using ICP data to provide early warning of deterioration and more accurate prognostication is an area of recent interest. In a retrospective analysis of 817 TBI patients, an automated computer algorithm was able to predict ICP crises with 30 min advance warning from previous ICP measurements and time since last episode of elevated ICP.[36] Another model using ICP and mean arterial blood

pressure as inputs also robustly predicted future increased ICP events 30 min in advance of their occurrence.[37] Although these computerized analyses in many ways simply confirm everyday clinical experience that patients with episodes of intracranial hypertension are at high risk of further ICP crises, they do also highlight potential for the development of widely applicable early warning systems of worsening brain state that could provide clinicians with time to intervene before irreversible secondary brain injury has occurred. Güiza *et al.*[38] used a novel approach to display the complexity and dynamic aspects of secondary insults of intracranial hypertension by displaying color-coded plots to summarize the relationship between ICP insults (defined by intensity and duration) with 6-month Glasgow Outcome Scale after TBI. Episodes of higher ICP were tolerated for shorter durations than more modestly elevated ICP, and impaired cerebrovascular autoregulation or reduced CPP reduced the ability of the brain to tolerate increases in ICP. These data support the dose of intracranial hypertension concept and highlight the importance of early intervention to reduce raised ICP, particularly if autoregulatory responses, as described in a subsequent section, are attenuated.

Cerebral Perfusion Pressure

CPP is calculated as the difference between mean arterial pressure and ICP and modifiable through manipulation of these variables.[35] Its accurate calculation requires the same zero reference point for both arterial pressure and ICP, *i.e.*, at the level of the brain using the tragus of the ear as the external landmark.[39] Head elevation is routinely used to optimize ICP after TBI, but hydrostatic effects mean that cerebral arterial blood pressure is reduced by a magnitude dependent on the degree of head elevation and distance between heart and brain reference points. In a patient with 30° head elevation, actual CPP may be up to 11 mmHg lower than calculated CPP if ICP is referenced to the level of brain and mean arterial pressure to the level of the heart.[40] Despite the crucial importance of the accurate assessment of CPP, a recent narrative review was unable to determine how mean arterial pressure was measured in the calculation of CPP in 50% of 32 widely cited studies of CPP–guided management.[41]

Consensus guidelines recommend that CPP should be maintained between 60 and 70 mmHg after TBI,[18] with evidence of adverse outcomes if CPP is lower or higher.[20] It is likely that the CPP threshold resulting in cerebral hypoperfusion and ischemia exists on an individual basis, and the concept of targeting an individualized "optimal" CPP range is gaining traction.[42]

Cerebral Autoregulation

In the healthy brain, cerebral autoregulation acts to maintain cerebral blood flow constant over a wide range of arterial blood pressure. Autoregulatory responses may be impaired after TBI and result in derangements in the relationships between regional cerebral blood flow and metabolic demand, thereby rendering the brain more susceptible to secondary ischemic insults. Although some degree of autoregulatory response is often maintained after TBI, it exists over a narrowed mean arterial pressure/CPP range, which can be identified by real-time measurement of cerebrovascular state.[43]

The pressure reactivity index is one of the most established methods to assess cerebral autoregulation continuously. It is calculated as the moving Pearson correlation coefficient between 30 consecutive, 10-s averaged values of ICP and arterial blood pressure over a 4-min period and varies between −1 and +1.[42] An inverse correlation between arterial pressure and ICP, indicated by a negative value for pressure reactivity index, represents normal cerebrovascular reactivity, whereas an increasingly positive pressure reactivity index defines a continuum of increasingly nonreactive cerebrovascular responses when changes in arterial blood pressure and ICP are in phase. Plotting pressure reactivity index against CPP results in a U-shaped curve in many patients, and the point where the pressure reactivity index is most negative represents optimal CPP, that is, the CPP range in which autoregulatory capacity is most preserved in that injured brain (fig. 1).[44] Targeting optimal CPP rather a generic CPP threshold avoids the risks of low CPP on the one hand and excessive CPP on the other and has been associated with improved outcomes in uncontrolled case series.[42,44] Abnormal autoregulation defined by pressure reactivity index monitoring is also a strong predictor of mortality and functional outcome after TBI.[45] In addition to allowing optimization of CPP, knowledge of the status of cerebrovascular reactivity also facilitates interpretation of the relationships between cerebral blood flow, oxygen delivery/demand, and cellular metabolism, and guides interventions targeted toward optimization of cerebral oxygenation and metabolic state.[46] Cerebrovascular reactivity can also be assessed using an oxygen reactivity index calculated as the moving correlation between brain tissue P_{O_2} and arterial blood pressure[47] and noninvasively using the correlation between arterial pressure and transcranial Doppler-derived mean blood flow velocity[48] or arterial pressure and several near infrared spectroscopy-derived variables.[49]

Standard methods of calculating the pressure reactivity index and other indices of autoregulatory reserve require high-frequency signal processing and automated analysis, which can be time consuming, costly, and not widely available. A recent study demonstrated that routine, minute-by-minute assessment of ICP and arterial blood pressure data contains relevant information for autoregulation monitoring.[50] In this study, a low-frequency autoregulation index, defined as the moving 1-min correlation of ICP and arterial blood pressure calculated over time intervals varying from 3 to 120 min, was able to identify optimal CPP recommendations that did not differ from those obtained using standard pressure reactivity index methodology. Further, because there is no requirement for high fidelity data collection and analysis with this methodology, there is less data "loss" and

therefore identification of optimal CPP during a higher proportion of monitoring time.

Another challenge in the search for reliable and accessible indices of cerebrovascular reactivity is the identification of appropriate analysis techniques that take account of the dynamic nonstationary, nonlinear nature of the measured signals that relate to autoregulation. Novel approaches such as wavelet analysis of slow wave oscillations in arterial blood pressure and near infrared spectroscopy-derived cerebral hemodynamic variables may overcome this issue.[51] Despite the intuitive good sense of targeting optimal CPP after TBI, there are currently insufficient high-quality data to recommend its routine clinical application.[52]

Cerebral Blood Flow

Alterations in cerebral blood flow in association with impairment of autoregulatory reserve may cause or worsen secondary ischemic brain injury after TBI. Cerebral blood flow may be determined directly or indirectly, although direct measurement at the bedside has proved challenging until recently.[53] Modern imaging techniques such as positron emission tomography and computed tomography perfusion provide detailed information about cerebral hemodynamics (and metabolism) over multiple regions of interest.[54] Although widely used as diagnostic and clinical research tools, imaging modalities are unable to provide continuous data for clinical monitoring that primarily relies on two methods for the continuous assessment of cerebral blood flow at the bedside.[53]

Transcranial Doppler Ultrasonography

Introduced in 1982, transcranial Doppler is a noninvasive technique that uses ultrasound waves to monitor blood flow velocity in large cerebral vessels by examining the Doppler shift caused by red blood cells moving through the field of view.[55] Transcranial Doppler measures relative rather than absolute flow, but there is a linear relationship between cerebral blood flow and flow velocity if vessel cross-sectional area and angle of insonation remain constant during the period of measurement. The transcranial Doppler waveform resembles an arterial pulse wave, which can be quantified by peak systolic, end diastolic and mean flow velocities, and the pulsatility index, which provides an assessment of distal cerebrovascular resistance. Although primarily used to detect and monitor cerebral vasospasm after aneurysmal subarachnoid hemorrhage, transcranial Doppler can detect inadequate cerebral blood flow, assess pressure autoregulation and CO_2 reactivity, determine response to therapeutic interventions, and offer prognostic information after TBI.[56] In a prospective, observational, multicenter study, early abnormalities in transcranial Doppler-derived pulsatility index and diastolic flow velocity had 80% sensitivity and 79% specificity for the prediction of subsequent neurologic deterioration in patients with mild and moderate TBI, with negative and positive predictive values of 98 and 18%, respectively.[57] As noted earlier, transcranial Doppler can also provide a noninvasive assessment of ICP, although the absolute accuracy of this technique is only ±15 mmHg, making it unsuitable for routine clinical use.[58]

The advantages of transcranial Doppler include its noninvasiveness and ability to provide real-time and continuous assessment of cerebral hemodynamics. Although it requires a degree of technical skill, there is reasonable interobserver agreement between transcranial Doppler measurements.[59]

Thermal Diffusion Flowmetry

Thermal diffusion flowmetry is an invasive, continuous, and quantitative monitor of regional cerebral blood flow.[60] The

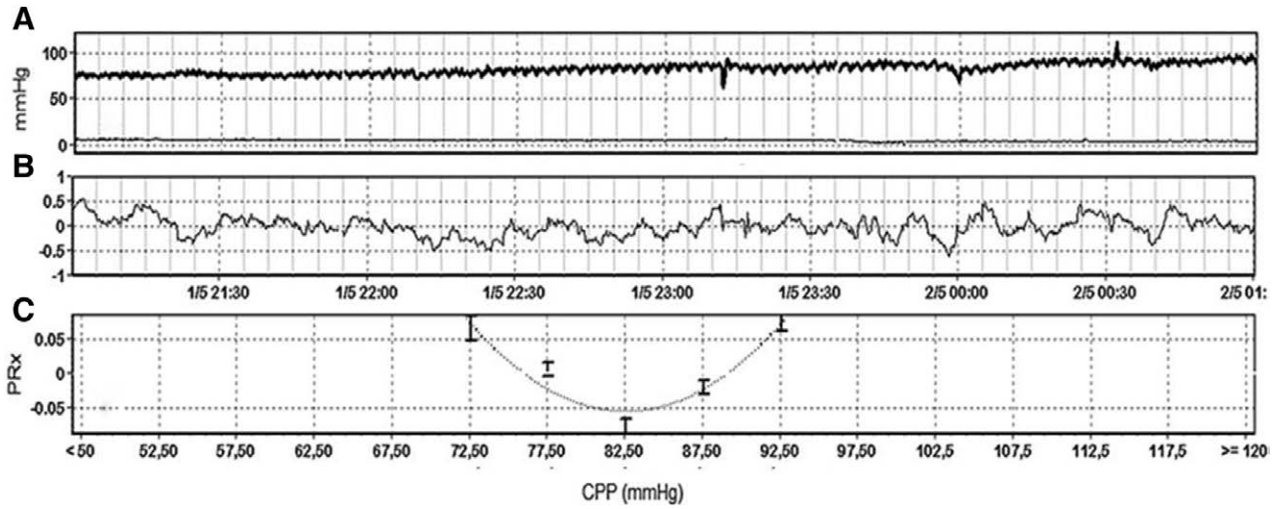

Fig. 1. Monitoring cerebrovascular reactivity to identify optimal cerebral perfusion pressure. This figure shows 4-h trend charts. (*A*) Cerebral perfusion pressure (CPP). (*B*) Pressure reactivity index (PRx). (*C*) PRx/CPP for evaluation of optimal CPP. Note the U-shaped relationship between CPP and PRx. The point where the PRx is most negative represents optimal CPP, the perfusion pressure range in which autoregulatory capacity is most preserved. Modified from figure by Dias *et al.*[44] with permission from Springer.

thermal diffusion flowmetry catheter consists of a thermistor heated to a few degrees above tissue temperature and a second, more proximal, temperature probe. The temperature difference between the two is a reflection of heat transfer that is converted into an absolute measurement of blood flow in ml · 100 g^{-1} · min^{-1}. The thermal diffusion flowmetry probe is sited in white matter, usually in an "at-risk" brain region where quantitative knowledge of perfusion is desirable. Thermal diffusion flowmetry can be used to detect changes in cerebral blood flow in real time, detect vasospasm in comatose patients, and assess autoregulation,[61] although there are limited clinical data using this technology and concerns over its reliability. It has been reported that thermal diffusion flowmetry provides useful data for only 30 to 40% of monitoring time because of monitor dysfunction secondary to placement errors and missing data during recalibrations.[53]

Cerebral Oxygenation

Although ICP and CPP are crucially important and routinely monitored variables after TBI, they provide limited assessment of the adequacy of cerebral perfusion. Cerebral ischemia is widely reported to occur despite ICP and CPP values that lie within accepted thresholds for normality.[62,63] Cerebral oxygenation monitoring provides information about the balance between cerebral oxygen delivery and utilization and therefore the adequacy of cerebral perfusion.[64]

Jugular Venous Oxygen Saturation

Jugular venous oxygen saturation can be measured by intermittent sampling from a catheter sited in the jugular bulb or continuously using a fiberoptic catheter. Jugular saturation monitoring is based on the simple principle that oxygen delivery and supply mismatch results in changes in oxygen extraction and therefore in jugular venous saturation (table 3).[65] The normal range of jugular venous oxygen saturation is 55 to 75%. Jugular desaturation is associated with worse outcome after TBI in a dose-dependent manner,[66] and guidelines recommend maintaining jugular saturation more than 50%, despite absence of evidence of benefit from jugular venous oxygen saturation–directed therapy.[18] On the other hand, elevated jugular venous oxygen saturation can be falsely reassuring because it may relate to scenarios associated with arteriovenous shunting or brain death when tissues are not metabolically active. In an early study, jugular venous oxygen saturation more than 75% occurred in almost 20% of 450 patients with severe TBI and was associated with worse outcomes compared to patients in whom jugular saturation was normal despite not being consistently related to either cerebral blood flow or CPP.[67]

Jugular venous oxygen saturation monitoring is dependent on technical aspects such as correct catheter placement to exclude the extracranial circulation. Sampling from the internal jugular vein with the dominant drainage, usually the right, is also recommended because oxygen saturation in the two jugular veins may be different.[68] Importantly, jugular venous oxygen saturation is a global, flow-weighted measure that may miss critical regional ischemia.[65] After early enthusiasm, its clinical use has decreased in favor of other methods of monitoring brain tissue oxygenation.[68]

Brain Tissue Oxygen Partial Pressure

Brain tissue P_{O_2} monitoring has the most robust evidence base of all bedside cerebral oxygenation monitoring techniques.[64] It is a focal measure so the utility of the technique is dependent on correct brain tissue P_{O_2} probe placement and knowledge of the location of the probe tip. Placement in at risk but viable subcortical white matter, such as perihematoma placement after TBI, is considered optimal,[69] although such precise placement can be technically challenging or impossible and risks inadvertent intralesional placement,

Table 3. Interpretation of Changes in Jugular Venous Oxygen Saturation

Jugular Venous Oxygen Saturation	Relative Changes in Cerebral Blood Flow and Oxygen Consumption	Causes
Low (< 50%)	↓ $CBF/CMRO_2$	• ↑ ICP • ↓ CPP • ↓ CBF • ↓ $Paco_2$ • ↓ Pao_2 • ↓↓ arterial blood pressure • ↑ $CMRO_2$ Seizures Pyrexia
Normal (55–75%)	CBF and $CMRO_2$ balanced	
High (> 80%)	↑ $CBF/CMRO_2$	• ↑ CBF - cerebral hyperemia • ↓ $CMRO_2$ • Failure of oxygen utilization (mitochondrial failure) • Arteriovenous shunting • Brain death

CBF = cerebral blood flow; $CMRO_2$ = cerebral metabolic rate for oxygen; CPP = cerebral perfusion pressure; ICP = intracranial pressure.

which yields useless information.[64] There is therefore an argument for routine probe placement in normal-appearing brain, typically in the nondominant frontal lobe, where it provides a reflection of global brain oxygenation.[69] Brain tissue P_{O_2} is a complex variable influenced by global determinants of oxygen delivery such as PaO_2, $PaCO_2$, FiO_2, arterial blood pressure, cardiac output, hemoglobin, and cardiorespiratory function, as well as by cerebral variables including ICP, CPP, autoregulation, metabolism, seizures, and cerebral tissue oxygen gradients (which are often increased in the injured brain).[64] Normal brain tissue P_{O_2} values range from 20 to 40 mmHg. In the clinical setting, values less than 15 to 20 mmHg are considered indicative of brain ischemia and below 10 mmHg of severe ischemia, although brain tissue P_{O_2} is best interpreted in the context of duration as well as depth of ischemia.[70]

Multiple studies have demonstrated an association between low brain tissue P_{O_2} and poor outcomes after TBI[71–73] independently of ICP and CPP.[63] Observational studies using historic controls suggest outcome benefits of supplementing ICP/CPP–guided management with brain tissue P_{O_2}–directed therapy to maintain brain tissue P_{O_2} more than 20 mmHg.[72,73] A systematic review of four studies incorporating 491 patients confirmed that brain tissue P_{O_2} and ICP/CPP–directed therapy combined is associated with superior outcomes compared to ICP/CPP–guided therapy alone, but all studies in this review were nonrandomized, and only two (with small sample sizes) were truly prospective.[74] Preliminary results have been released from a prospective, phase II randomized controlled trial (the brain tissue oxygen monitoring in traumatic brain injury–2 study) in which 110 patients with severe TBI were randomized to receive treatment guided by ICP monitoring alone or by brain tissue P_{O_2} and ICP monitoring according a prespecified protocol to maintain brain tissue P_{O_2} more than 20 mmHg and ICP less than 20 mmHg.[75] Compared to ICP–guided therapy, the combination of ICP and brain tissue P_{O_2}–directed therapy resulted in reduced time with brain tissue P_{O_2} less than 20 mmHg and was associated with a nonsignificant trend toward lower overall mortality and poor outcomes (although the study was not powered for outcome). In a more recent prospective multicenter study of 50 patients with moderate and severe TBI, brain tissue P_{O_2}/ICP–guided therapy was associated with a significant reduction in mortality at 3 and 6 months after injury compared to ICP–guided therapy alone.[71] Although there was no absolute difference in functional outcomes between the two groups in this study, patients in the brain tissue P_{O_2}-guided group had a 1.8 to 2.9 times higher rate of more favorable outcome between 1 and 6 months postinjury compared to those in the ICP–guided group. Further adequately powered, prospective studies are required to identify the effects of brain tissue P_{O_2} monitoring–guided therapy on TBI outcomes.

Recent guidelines recommend interventions to maintain brain tissue P_{O_2} more than 20 mmHg after TBI.[76] Brain hypoxia can be reversed by several factors including optimization of mean arterial pressure, CPP, PaO_2, $PaCO_2$, and hemoglobin concentration,[77] but which intervention or combination of interventions should be used to reverse reduced brain tissue P_{O_2} is undefined. The responsiveness of brain tissue hypoxia to a given intervention, rather than the nature of the intervention, appears to be the prognostic factor with reversal of hypoxia being associated with reduced mortality.[78] Although brain tissue P_{O_2} can be normalized by incremental increases in FiO_2, reliance on this intervention is unlikely to be the solution because hyperoxia can lead to increased cerebral excitotoxicity and potentially aggravate secondary brain damage independent of brain tissue P_{O_2}.[79]

Near Infrared Spectroscopy

Near infrared spectroscopy is a noninvasive technique based on the transmission and absorption of near infrared light (700 to 950 nm) as it passes through tissue. Oxygenated and deoxygenated hemoglobin have characteristic and different absorption spectra in the near infrared, and their relative concentrations in tissue can be determined by their absorption of light in this wavelength range.[80] Near infrared spectroscopy-based cerebral oximeters derive a scaled absolute hemoglobin concentration (the relative proportions of oxy- and deoxyhemoglobin in the field of view) from which regional cerebral tissue oxygen saturation is calculated. This is largely, but not exclusively, sensitive to oxygen extraction and therefore provides regional assessment of critical oxygen supply/demand mismatch. The "normal" range of regional cerebral oxygen saturation is reported to lie between 60 and 75%, but there is substantial intra- and interindividual variability in near infrared spectroscopy–derived cerebral saturation and no validated regional cerebral saturation-defined ischemic thresholds to guide therapeutic interventions.[81] Low regional cerebral oxygen saturation values have been associated with poor outcome in small case series,[82] and near infrared spectroscopy has been used to determine optimal CPP noninvasively.[83] However, there are limited high-quality data on the application of near infrared spectroscopy for monitoring after TBI, and no outcome studies investigating near infrared spectroscopy-guided management.[49] In the research setting, near infrared spectroscopy-monitored changes in the oxidation state of oxidized cytochrome *c* oxidase, the final electron acceptor in the mitochondrial electron transport chain responsible for more than 95% of oxygen metabolism, provides additional information about cellular energy status and may aid in the determination of near infrared spectroscopy-defined ischemic thresholds.[84]

The near infrared spectroscopy technique has several confounders including potential signal contamination from extracranial tissue.[80] The presence of intracranial hematoma, cerebral edema, or traumatic subarachnoid hemorrhage might also invalidate some of the assumptions upon which near infrared spectroscopy algorithms are based, but this has been used to advantage in the development of a handheld

device to screen for traumatic intracranial haematomas in prehospital environments.[85] Technologic advances, including the development of frequency (or domain) and time-resolved spectroscopy systems, have allowed measurement of absolute chromophore concentration with obvious advantages for clinical applications.[81] Diffuse correlation spectroscopy provides noninvasive measures of cerebral blood flow in addition to cerebral tissue oxygen saturation and the potential to derive cerebral metabolic rate.[86] Although the future holds promise for the development of a single near infrared spectroscopy device with capability to noninvasively measure cerebral hemodynamics, oxygenation, and metabolism over multiple regions of interest,[87] routine near infrared spectroscopy monitoring is currently not recommended in adult TBI patients.[49]

Brain Metabolism and Biochemistry

Cerebral microdialysis is a well established laboratory technique that was introduced into clinical practice during the 1990s to monitor brain tissue chemistry. The tip of a microdialysis catheter incorporates a semipermeable dialysis membrane, and diffusion drives the passage of molecules across the membrane along their concentration gradient from the brain extracellular fluid into the isotonic dialysis fluid (fig. 2).[88] The concentrations of clinically relevant compounds that accumulate in the dialysate are measured in a semiautomated calorimetric bedside analyzer, usually at hourly intervals.[89] Clinical microdialysis catheters have a molecular weight cutoff of 20 kDa and are suitable for recovery of small molecules including glucose, lactate, pyruvate, glycerol, and glutamate.[90] Each of these, and the lactate:pyruvate ratio, is a marker of a particular cellular process associated with glucose metabolism, hypoxia/ischemia, and cellular energy failure (fig. 2). The microdialysis catheter is placed in at-risk brain tissue so that biochemical changes in the area of brain most vulnerable to secondary insults can be monitored.[90]

Energy dysfunction is increasingly recognized as a key factor in the pathophysiology of TBI.[91] Imbalance in the supply and demand for glucose can trigger a cerebral metabolic crisis from ischemic and nonischemic causes, and cerebral microdialysis is unique among bedside neuromonitoring techniques in that it is able to identify both.[92] Increased lactate:pyruvate ratio in the presence of low pyruvate indicates a profound reduction in energy substrate supply and classic ischemia, whereas elevated lactate:pyruvate ratio in the presence of normal or high pyruvate indicates a nonischemic cause related to mitochondrial dysfunction with or without increased metabolic demand.[93] Cerebral microdialysis-monitored glutamate is a marker of hypoxia/ischemia and excitotoxicity,[94] and glycerol is a (nonspecific) marker of hypoxia/ischemia-related cell membrane breakdown.[95] Because microdialysis measures changes at the cellular level, it has the potential to identify cerebral compromise before changes in other monitored variables.[96]

Expert consensus recommendations for the clinical application of cerebral microdialysis have recently been published, although there is no evidence that microdialysis-guided therapy improves outcomes.[90] Periods of low brain glucose concentration (less than 0.7 to 1 mM) combined with elevated lactate:pyruvate ratio (more than 40) suggest severe hypoxia/ischemia and correlate with poor outcome.[97] After TBI, the normal relationship between serum glucose concentration, glycemic control, and brain glucose may be lost, and brain glucose may fall to levels that are insufficient to meet metabolic demand even when serum glucose concentration is within a normal range.[98] This phenomenon is referred to as neuroglycopenia and is the origin of a nonhypoxic metabolic crisis. If brain extracellular fluid glucose concentration is very low (0.2 mM), a trial of increasing serum glucose concentration (even if within normal limits) has been recommended to minimize the burden of neuroglypenia.[90] The lactate:pyruvate ratio has been used to guide CPP management,[99] although some studies have found that

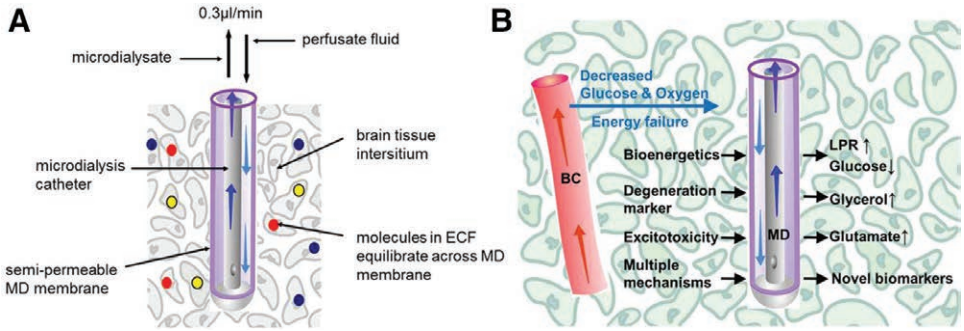

Fig. 2. Principle of cerebral microdialysis (MD) monitoring. (*A*) The MD catheter is located in at-risk brain tissue. Isotonic fluid is pumped through the MD catheter at a rate of 0.3 µl/min. Molecules at high concentration in the brain extracellular fluid (ECF) equilibrate across the semipermeable MD membrane into the microdialysate, which is collected for subsequent analysis. (*B*) The effects of decreased brain glucose and oxygen supply and cellular energy failure can be monitored by the bedside measurement of biomarkers of bioenergetics, cellular degeneration, and excitotoxicty. Additional, novel biomarkers can be measured in the research setting. BC = blood capillary; LPR = lactate:pyruvate ratio. Modified from figure by Kirkman and Smith[88] with permission from Elsevier.

elevated lactate:pyruvate ratio can occur despite CPP values that are customarily considered to be adequate.[100] This is unsurprising given the nonischemic causes of elevated lactate:pyruvate ratio, and further highlights the importance of using multimodality physiologic data to inform individualized treatment strategies.

The dialysate provides a facsimile of brain extracellular fluid because it contains all molecules small enough to pass through the microdialysis membrane. Macromolecules can be sampled for research purposes using high-molecular-weight cutoff (100 kDa) dialysis membranes. Several novel biomarkers, including S100B,[101] nitric-oxide metabolites,[102] and *N*-acetylaspartate,[103] have been investigated, as have TBI-related inflammatory processes *via* the temporal profile of multiple cytokines.[104] Metabolic distress after TBI is associated with a differential proteome indicating cellular destruction,[105] and incorporation of proteomics into the microdialysis technique has potential to provide new insights into the pathophysiology of brain injury. Cerebral microdialysis can also provide unique information during neuroprotective drug trials, establishing whether systemically administered agents cross the blood–brain barrier to their site of action and monitoring the downstream effects of drug actions directly.[89]

The only commercially available clinical microdialysis system has limited temporal resolution,[89] and this may miss short-lived but important changes in brain tissue chemistry, including those induced by electrophysiologic abnormalities such as cortical spreading depolarizations.[106] A continuous rapid-sampling cerebral microdialysis technique that allows online measurement of potassium, glucose, and lactate but not pyruvate has been described for research use.[107]

Despite evidence from large numbers of studies confirming that abnormal brain chemistry relates to poor outcomes after TBI, the clinical utility of cerebral microdialysis-guided therapy is still debated.[90] Further studies are required to determine the effectiveness of microdialysis-guided clinical decision-making as part of multimodality monitoring paradigms.

Electroencephalography

Seizures occur in 20 to 40% of TBI patients, and early detection and treatment are crucial to minimize the burden of seizure-related secondary injury. Intermittent electroencephalography (EEG) has historically been used for the diagnosis of seizures and status epilepticus, but continuous EEG monitoring is now recommended for the detection of posttraumatic seizures and to guide anticonvulsant therapy because of the high incidence of nonconvulsive seizures after TBI.[6,108] Integration of continuous EEG into multimodal neuromonitoring strategies identifies associations between seizures, intracranial hypertension, and cerebral metabolic derangements[109] and offers prognostic information.[75] Continuous EEG monitoring is a resource-intense technology requiring specialized technicians for application and maintenance of electrodes and neurophysiologists for interpretation of EEG recordings.[110] Telemedicine allows interpretation away from the bedside and may facilitate the adoption of continuous EEG, as might the development of automated seizure detection software.[75]

Invasive EEG monitoring using subdural strip or intracortical depth electrodes allows detection of seizures that are not visible on standard (scalp) EEG monitoring.[111] In a small prospective multicenter study, more than 40% of EEG-defined seizures or periodic discharges were detected only by intracortical depth electrodes.[106] Cortical spreading depolarizations, an important cause of secondary brain injury, have been identified in more than half of TBI patients using invasive continuous EEG monitoring.[112] They are associated with unfavorable outcomes, but a definite causal relationship between spreading depolarizations and outcome has yet to be established. Further research is required to determine whether therapies to prevent or treat these electrophysiologic abnormalities limit brain injury progression and improve outcomes. Spreading depolarizations can currently only be detected by invasive EEG monitoring, but developments in scalp EEG and noninvasive technologies that measure surrogates of regional cerebral blood flow (such as near infrared spectroscopy) are likely to lead to the introduction of noninvasive methods for their detection.

Integrating Multimodality Neuromonitoring Data

Despite the many benefits of multimodality neuromonitoring after TBI, including insights into the mechanisms of secondary brain injury, identification of deterioration in brain state, and guidance of individualized therapeutic interventions, the adoption of monitoring strategies is highly variable between centers.[6] Simple approaches are most likely to gain traction in the clinical setting, and the simultaneous measurement of ICP and brain tissue P_{O_2} is a logical approach aided by the availability of a single probe capable of monitoring both.[113]

Because of the number and complexity of monitored physiologic variables and the interplay between them, computational analysis and integration of data are essential prerequisites for the presentation of user-friendly and clinically relevant information at the bedside.[114] Commercial systems are available to process and display multiple data streams, although many systems in clinical use have been designed around the needs of individual institutions or researchers.[115] Several challenges hinder data integration and interpretation, including situations where one or more variables remain normal in the face of derangements in another. One area of particular uncertainty is what, if any, action should be taken in response to increases in ICP in the context of normal brain tissue oxygenation or metabolism.[35] Advanced mathematical tools can be applied to large volumes of clinical physiologic data with the goals of artifact removal and identification of more specific markers of secondary brain

injury.[114] An alternative approach incorporates computational model interpretation of complex multimodal data sets to provide summary outputs of patient-specific simulations of brain state that can guide individualized clinical decision making and also generate clinically important but currently unmeasured variables such as cerebral metabolism.[116]

Future Directions

Although there is substantial evidence that multimodality neuromonitoring-guided therapy results in improvements in cerebral physiology, high-quality evidence that this translates into beneficial effects on clinical outcomes remains elusive. Neuromonitoring can only modulate patient outcome if a monitor-detected change in physiology prompts timely and appropriate therapeutic intervention to reverse an abnormality that is itself an integral determinant of outcome.[117] It has been suggested that interventions that result in transition from an abnormal to normal brain state are more likely to be efficacious than those focusing on response to individual thresholds.[118] Furthermore, thresholds for intervention and optimal therapeutic interventions in response to changes in monitored variables remain undefined in many circumstances. It is also unclear whether all TBI patients can benefit from neuromonitoring, although it seems plausible that those with certain injuries or physiologic phenotypes might have the most to gain from neuromonitor-guided interventions. Incorporating patient demographics and brain imaging with multimodality neuromonitoring strategies might better optimize individualized treatment decisions. A pragmatic approach to identify those who might benefit from ICP monitoring, combining clinical and cranial computed tomography scan findings, has been suggested.[19]

There are substantial challenges in the conduct of robust prospective outcome studies to establish whether adoption of a multimodal neuromonitoring strategy is beneficial, and multiple examples in TBI research of promising results from single-center studies failing to translate into evidence of benefit in subsequent multicenter trials.[119] Study design and conduct are clearly of crucial importance in this regard. The ideal neuromonitoring study would be one in which all participants underwent the monitoring modality under investigation with some randomized to receive monitor-guided therapy and others to standard care, with standardization of treatments across centers. However, ensuring such homogeneity between centers, not only in monitor-defined therapeutic thresholds but also in all applied treatments, is a major challenge. Even well conducted studies with clearly defined treatment protocols have reported treatment variations between centers, which may have influenced the results.[120] Other key limitations in demonstrating the efficacy of neuromonitoring are the heterogeneity of pathophysiologic changes after TBI and the need for complex and multiple therapeutic interventions in the absence of a single intervention that is unequivocally associated with improved outcomes.[121] Which monitored variables are modifiable targets for treatment and which are simply markers of injury severity also remain unclear. Furthermore, TBI does not represent a single pathophysiologic entity but a complicated and heterogeneous set of disease processes with substantial temporal and regional heterogeneity. It is also not clear whether different forms of TBI, such as traumatic hematoma and diffuse axonal injury, should be treated differently. Finally, it can be argued that there is no longer clinical equipoise to conduct randomized studies in which some patients may not receive low-risk, potentially high-yield monitor-guided interventions that are now considered standards of care by many.

The failure of recent high-profile therapeutic clinical trials has raised questions as to whether randomized controlled trials are appropriate instruments to assess a condition as heterogeneous as TBI, and it has been suggested that there should be a paradigm shift in TBI research to incorporate concepts such as precision medicine and comparative effectiveness research.[122] The International Initiative for Traumatic Brain Injury Research is a global collaboration that aims to revolutionize the study of TBI by international collaboration, coordination of standardized date collection, and big-data sharing.[123] It remains to be seen whether this approach will resolve the outstanding questions about the roles and indications for neuromonitoring after TBI and demonstrate unequivocally whether monitor-guided interventions lead to improved outcomes for patients.

Competing Interests

The author declares no competing interests.

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