

Physiological Monitoring of the Severe Traumatic Brain Injury Patient in the Intensive Care Unit

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Abstract Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. Despite encouraging animal research, pharmacological agents and neuroprotectants have disappointed in the clinical environment. Current TBI management therefore is directed towards identification, prevention, and treatment of secondary cerebral insults that are known to exacerbate outcome after injury. This strategy is based on a variety of monitoring techniques that include the neurological examination, imaging, laboratory analysis, and physiological monitoring of the brain and other organ systems used to guide therapeutic interventions. Recent clinical series suggest that TBI management informed by multimodality monitoring is associated with improved patient outcome, in part because care is provided in a patient-specific manner. In this review we discuss physiological monitoring of the brain after TBI and the emerging field of neurocritical care bioinformatics.

Keywords Traumatic brain injury · Monitor · Intracranial pressure · Brain oxygen · EEG · Microdialysis

Introduction

Every 15 s someone suffers a traumatic brain injury (TBI) in the USA. It is estimated that 2 % of the US population lives with a TBI-related disability, and TBI causes more deaths in men under 35 years old than all other diseases combined. Despite much research and success in animal models, effective drug therapies have not been identified in clinical trials

[1•]. Instead much of TBI care in the intensive care unit (ICU) is centered on the early identification and removal of mass lesions and on the detection, prevention, and management of secondary brain insults which adversely affect outcome (e.g., hypotension, hypoxia, seizures, and elevated intracranial pressure, ICP). TBI is a heterogeneous disease in cause, pathological features, severity, and prognosis. Consequently, TBI care depends in large part on careful and repeated assessment of clinical and laboratory findings, imaging studies, and bedside physiological data.

The “ideal” monitor (Table 1) of neurological function in the ICU does not yet exist, although a variety of monitors are in clinical use (Table 2). These monitors can be broadly classified into two broad categories: (1) radiographic or tomographic techniques that provide a snapshot in time and (2) bedside monitors, which in turn may be subdivided into monitors that are (a) invasive or noninvasive or (b) continuous or noncontinuous. Ideally, more than one monitor is used since the brain is a complex organ and no single method can provide complete information about the health of the brain. This concept of “multimodality monitoring”—defined as the simultaneous collection of data from multiple diverse sources associated with a single patient coupled with the ability to view the data in an integrated and time-synchronized manner—has evolved in recent years in parallel with the evolution of bioinformatics, but its use is still in its infancy. The primary purpose of multimodality monitoring is to better understand what is going on within the brain of a patient to target and individualize treatment more appropriately. In turn, monitoring permits early neurological worsening to be detected before irreversible brain damage occurs and can help guide patient management, e.g., monitor the therapeutic response of some interventions or avoid any adverse effects of management.

Monitoring by itself does not alter outcome. Instead it is how the information is used that contributes to patient wellbeing,

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Table 1 The ideal monitor

Provides functional data
Provides regional and global information
Portable
Provides point-of-care measurement
High spatial resolution
High temporal resolution
Continuous or frequently repeatable
Does not interfere with patient care
Noninvasive
Reliable and reproducible quantitative data
Not operator-dependent
Easy to use; requires little training to use
Suggests a cause and appropriate treatment

particularly when targeted to patient-specific pathophysiology. In this article, we will briefly review physiological monitors of the brain that can be used in the ICU, including (1) ICP, (2) monitors of cerebral oxygenation, including direct measurement of brain oxygen (partial pressure of brain tissue O_2 , $PbtO_2$), jugular venous catheters, and near-infrared spectroscopy (NIRS), (3) metabolic monitors, i.e., cerebral microdialysis (CMD), (4) cerebral blood flow (CBF) monitors such as transcranial Doppler (TCD) ultrasonography, thermal diffusion (TD) flowmetry, and laser Doppler flowmetry (LDF), and (5) electrophysiological tools such as evoked potentials and electroencephalography (EEG). In addition we will briefly mention the neurological evaluation and biomarkers, specifically biosamples. Although important in complementing or supplementing physiologic data, a review of brain imaging studies that provide anatomic information (e.g., CT, MRI, or their derivatives CT angiography and magnetic resonance angiography, and perfusion studies; tomographic evaluation, e.g., PET or single photon emission scintigraphy, and monitoring of extracerebral organ

Table 2 Monitors in clinical use

Clinical evaluation, serial assessment
Systemic: BP, O_2 saturation, $EtCO_2$, temperature
Hydraulic: ICP/ CPP
Electrophysiology: EEG, SSEP, BAER
Radiographic/tomographic: PET, SPECT, CT-perfusion, stable xenon-enhanced CT (^{133}Xe), MRI
CBF: TCD ultrasonography, laser Doppler flowmetry, thermal diffusion probe, transcranial cerebral oximetry
Metabolic: Microdialysis, jugular venous oximetry, direct brain oxygen, NIRS

BP blood pressure, *EtCO₂* end-tidal CO_2 concentration, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *EEG* electroencephalography, *SSEP* somatosensory evoked potentials, *BAER* brainstem auditory evoked response, *SPECT* single photon emission scintigraphy, *CBF* cerebral blood flow, *TCD* transcranial Doppler, *NIRS* near-infrared spectroscopy

systems) is beyond the scope of this review. Table 3 lists what “should” be monitored in the TBI patient in an “ideal” present-day ICU.

Neurological Examination

Sequential clinical evaluation is central to physiologic monitoring of the TBI patient in the ICU. It is most informative when the patient is resuscitated, i.e., normal oxygenation and arterial pressure. In addition, clinical assessment depends on the temperature of the patient and pharmacological agents such as sedatives, analgesics, and muscle relaxants, all of which may influence the neurological condition. The most important aspect of the clinical examination is assessment of consciousness and awareness; this allows coma or delirium to be detected. Consciousness is examined by the response to verbal or noxious stimuli and depends, in large part, on verbal, eye, or motor responses. The Glasgow Coma Scale (GCS) [2] can be used to evaluate consciousness since it is objective and allows sequential testing with reasonable interobserver and intraobserver reliability. Coma is defined as the absence of arousal and of awareness or a GCS score of 8 or less. The full outline of unresponsiveness (FOUR) score [3], which includes pupillary light and corneal reflexes and breathing pattern examination, may also be used to assess consciousness. Delirium is defined as a fluctuating condition characterized by altered attention, spatio-temporal disorientation, disorganized thinking, and altered awareness. It may be assessed using a variety of scales, e.g., the confusion assessment method for the ICU [4] or the ICU delirium screening checklist [5]. Further assessment then depends on what pharmacological agents are in use and whether the patient is mechanically ventilated, but at the very least, a directed examination as part of sequential evaluation will include the pupils and symmetry of motor responses.

Table 3 What do I really want to know?

Anatomy
Head CT
Pressure: ICP, MABP, and CPP
Brain + blood + CSF
Flow: CBF
Metabolism
Oxygen, glucose
Function (backend monitor)
Neurological examination
SSEP or EEG
Biomarkers (e.g., GFAP, NF, glycerol)

MABP mean arterial blood pressure, *GFAP* glial fibrillary acidic protein, *NF* neurofilaments

Intracranial Pressure

Monitoring ICP and cerebral perfusion pressure (CPP; mean arterial blood pressure, MABP, minus ICP), should be considered in all patients with severe TBI (GCS score of 8 or less) particularly when the admission head CT scan is abnormal [6]. There are presently no reliable noninvasive ICP monitors. However, in select patients, noninvasive techniques, e.g., using the TCD ultrasonography derived pulsatility index [7] or optic nerve ultrasonography [8•], can be used as a screening tool for elevated ICP. ICP is best monitored invasively, with a ventricular catheter or an intraparenchymal monitor [6, 9]. These devices are usually placed by neurosurgeons, but in some institutions, neurointensivists insert ICP monitors with neurosurgical backup [10]. Hemorrhage is the commonest procedural complication and is identified in 1 % of parenchymal monitors and 5 % of ventriculostomies. Most of these are identified on imaging and are not of clinical importance. An international normalized ratio of 1.6 or less and a platelet count of more than 100,000 are necessary to safely place an ICP monitor.

The most commonly used ICP monitors include a ventriculostomy, the Camino or the Ventrix (Integra Neurosciences, Plainsboro, NJ, USA), the Codman microsensor (Codman, Raynham, MA, USA), the Spiegelberg ICP sensor and compliance device (Spiegelberg, Hamburg, Germany), and the Raumedic ICP sensor and multiparameter probe (Raumedic, Münchberg, Germany). A ventriculostomy or external ventricular drain (EVD) to monitor ICP also allows therapeutic drainage of CSF to control elevated ICP [11]. However, an EVD may be difficult to insert after TBI because of small ventricular size or shift. In addition, a traditional EVD with an external transducer only allows intermittent ICP measurements when the drain is closed. In newer commercially available catheters that have a pressure transducer within their lumen, simultaneous ICP monitoring and CSF drainage is feasible but an EVD can miss episodes of increased ICP when it is draining [12, 13•]. The catheter can become blocked by blood or debris, and flushing with 1–2 ml of normal saline may be needed to restore catheter patency. This and other catheter manipulations, and in particular routine CSF sampling, increases the risk of infection that occurs in 5–20 % of patients [14, 15].

Intraparenchymal ICP monitors are easier to place than EVDs and provide continuous ICP recording. There are several different intraparenchymal technologies, including fiberoptic, strain gauge, and pneumatic technologies. These devices are usually inserted through a small burr hole into the brain parenchyma in the nondominant frontal lobe in diffuse injuries or on the side of maximal injury when there is focal abnormality. ICP should be interpreted with the clinical examination and imaging studies. A specifically designed “bolt” in the skull that may also permit insertion

of other monitors (e.g., brain oxygen, brain temperature, microdialysis, and CBF) secures these monitors in place. The risks associated with intraparenchymal ICP monitors are less than those associated with EVDs; hemorrhage occurs in about 1 % of devices and infections occurs less frequently. Technical complications, e.g., catheter breakage or dislodgement, may occur in about 4 % of cases. These often occur during transport, nursing maneuvers, or patient activities but generally, if recognized, are of little clinical consequence.

There is a well-described relationship between mortality and increased ICP (more than 20 mmHg) in TBI patients [16–19]. Even brief episodes of elevated ICP can adversely affect outcome [20•]. Similarly, elevated ICP that does not respond to treatment is associated with a significantly increased risk of death [21]. However, whether ICP treatment makes a difference to outcome remains unclear since ICP treatment is largely phenomenological rather than mechanistic. The effect of outcome therefore depends in part on how effective the treatment for increased ICP is and any potential adverse effect associated with the treatment. In a recent meta-analysis that included more than 120,000 TBI patients Stein et al. [22] found that ICP monitoring and treatment was associated with better outcome. Some studies, however, question how an ICP monitor influences outcome [23–25].

In the neurocritical care unit (NCCU), ICP is best treated with an ICP monitor in place since it is difficult to diagnose elevated ICP by clinical means alone. In addition, findings on an admission CT scan suggest who is at risk of increased ICP, but the relationship between these CT findings and the subsequent ICP course during ICU care is not reliable [26•]. Results from a recent NIH-sponsored randomized trial in Latin America also suggest that an ICP monitor helps improve the efficiency of care (Chesnut R, University of Washington, personal communication 2012). The current consensus is to treat ICP that is greater than 20 mmHg [6]. This is based largely on an understanding of the Monro–Kellie doctrine and is supported by clinical observations and physiological data. However, this treatment of ICP when a numerical threshold is reached may be an oversimplification since hypoxia or cellular dysfunction in the brain may still occur when ICP is normal (less than 20 mmHg) [27–30, 31••, 32]. Instead, ICP may be better managed when considered in the context of (1) compliance, (2) ICP waveform morphology, (3) cerebral autoregulation (CAR), and (4) impact of ICP on CBF and brain metabolism [33].

Compliance and Elastance

From the Monro–Kellie doctrine, the brain is able to compensate for a volume increase in one of the compartments with

volume changes in the others. When these compensatory mechanisms fail, small volume changes can cause significant ICP increases or even herniation. To quantify this compensatory ability, or compliance, a reproducible volume challenge, e.g., injection of a small (1-ml) fluid volume through an EVD and a measure of the ICP change are needed [34]. The ICP response provides the volume–pressure response ($VPR = ICP \text{ change}/\text{volume change}$). Logarithmic conversion of the VPR defines the volume change that would produce a tenfold ICP increase [35]; this is known as the pressure–volume index (PVI). The normal PVI is between 25 and 30 ml. However, VPR or PVI is rarely calculated in clinical practice since to do so requires injection of volume through an EVD that may contribute to infection or intracranial hypertension. Instead, compliance and compensatory reserve may be examined through ICP waveform analysis or with derived indices such as the index of pressure–volume compensatory reserve (RAP), defined as the correlation coefficient (R) between the pulse pulsation amplitude (A) and mean ICP (P) [36, 37]. The RAP index is based on the concept that with each heart beat a small volume increase occurs in the intracranial compartment. RAP values range between -1 and $+1$. Higher values up to $+1$ indicate that the pulse pulsation amplitude varies directly with ICP, i.e., poor compliance. In the ICP waveform the most prominent wavelets are marked P_1 , P_2 , and P_3 . With good compliance, P_1 is the highest wavelet. The P_2 amplitude increases as compliance decreases, often before an increase in ICP occurs, and eventually the P_2 wavelet may equal or exceed P_1 and the ICP waveform resembles the arterial pulse waveform. Finally, the brain's compensatory reserve may be estimated from the therapeutic intensity level (TIL). This is quantification of what treatment is needed to control ICP [38]; a greater TIL implies worse compliance. Exactly how these measures (waveform analysis, TIL, RAP, or PVI) should be used in TBI management is still being elucidated. However, a patient with abnormal compliance or ICP waveform but normal ICP may require greater watchfulness or different treatment compared with a patient with normal ICP and a normal waveform or even a patient with slightly elevated ICP and normal compliance.

Autoregulation

The healthy brain is able to maintain a constant CBF across MABP ranges of 40–160 mmHg through CAR. In TBI, autoregulation is often compromised both regionally and globally and there can be substantial variability between individuals. Autoregulation can be tested using TCD ultrasonography to examine blood flow velocity (BFV) changes resulting from changes in MABP. The autoregulatory index (ARI) can be calculated as $ARI = \Delta CVR (\%) / \Delta MABP (\%)$, where CVR is cerebrovascular resistance. The CVR is calculated as $MABP/BFV$. Alternatively, a measure of CAR may be obtained through the cerebrovascular pressure reactivity index

(PRx) [39]. PRx is a linear correlation coefficient between average arterial blood pressure and ICP over 3–4 min. PRx is negative when CAR is intact but when CAR is compromised or lost, PRx is positive since ICP follows MABP. Several observational studies suggest an association between poor CAR and poor outcome [40, 41]. However, how best to use the information about CAR in the management of TBI is still being elucidated. The relevance of dynamic testing (CAR, PRx, RAP) is to facilitate individualized management and not to set thresholds applicable to all patients, e.g., determining the optimal level of CPP [42, 43].

Cerebral Perfusion Pressure

CPP is an important driving force behind CBF. Much of TBI care in the NCCU depends on ensuring an adequate CPP, the principal determinants of which are MABP and ICP; i.e., calculation of CPP requires measurement of ICP with a monitor. In addition, accurate measurement of MABP is necessary. This may be accomplished through an arterial pressure catheter (indwelling arterial line) or noninvasively. The position of an arterial pressure transducer, i.e., at the level of the foramen of Monroe or the heart, remains in debate [44•]; this can influence threshold values.

Under normal physiological conditions in the adult, CPP is 70–85 mmHg, although true CPP may vary by up to 30 mmHg [45, 46]. A minimum CPP threshold of 60 mmHg is generally accepted in TBI patients. However, brain hypoxia may still occur despite an adequate CPP [27, 28], and augmenting CPP does not always translate into improved outcome [47]. In addition, the optimal CPP is debated, and it may vary in each patient and over time in an individual, whereas the relationship between ICP and CPP depends in part on the state of autoregulation [48]. Therefore, threshold-based treatment, i.e., treat when ICP is greater than 20 mmHg or when CPP is less than 60 mmHg, may be an oversimplification. Recent advances in data processing and computerized bedside monitoring now make it possible to perform online, real-time analysis of the derived indices PRx or RAP [40, 41] and in turn calculation of optimal CPP. Alternatively, use of other monitors, e.g., microdialysis or brain oxygen to supplement ICP and CPP data (multimodality monitoring), may help determine an individual patient's optimal CPP [49]. Clinical studies suggest that the incidence of favorable outcome after TBI is increased when median CPP is close to optimal CPP [50••].

Cerebral Blood Flow

Transcranial Doppler Ultrasonography

TCD ultrasonography combines ultrasound, usually at a frequency of 2 MHz, and the Doppler principle (i.e., changes in

the frequency of sound when it is reflected by a moving object) to determine the velocity of blood (cm/s) in a given insonated artery, usually the proximal arteries of the circle of Willis. The main advantage of TCD ultrasonography is that it is noninvasive. However, the quality of the TCD signal is operator-dependent, and in about 10 % of patients insonation of the basal vessels is not feasible. Accurate interpretation of the TCD signal also depends on patient age, sex, hematocrit, partial pressure of CO₂, and blood pressure.

TCD ultrasonography provides real-time dynamic information about BFV. It is not a quantitative CBF monitor in milliliters per 100 g per minute [51]; instead, TCD ultrasonography provides information about the presence and character of flow, and tracks relative change in flow when the vessel diameter is constant. Mean BFV is directly proportional to flow and inversely proportional to the cross-sectional area of the vessel. When the vessel caliber decreases, BFV increases in the face of decreasing CBF; hence, TCD ultrasonography is often used to monitor the time course of vasospasm in patients with aneurysmal subarachnoid hemorrhage (SAH) [52, 53]. It is most accurate for middle cerebral artery vasospasm, where a mean middle cerebral artery BFV less than 120 cm/s excludes clinically significant vasospasm whereas a BFV greater than 180 cm/s indicates severe vasospasm. Hyperemia, which may be used to treat vasospasm, may also increase BFV. To differentiate vasospasm from hyperemia, BFV in the intracranial circulation is compared with BFV in the extracranial internal carotid artery (Lindegaard ratio). When the ratio is less than 3, vasospasm is unlikely, whereas a ratio greater than 6 is associated with severe angiographic vasospasm [54].

There are several uses for TCD ultrasonography in the TBI patient: (1) noninvasive estimation of ICP, e.g., in coagulopathic patients [55], (2) evaluation of CAR or vasomotor reactivity [56–61], (3) detection and monitoring emboli that may be helpful after blunt cerebrovascular injury or vessel dissection [62], and (4) to help diagnose brain death by identification of intracranial circulatory arrest [63].

Thermal Diffusion Flowmetry

TD flowmetry provides continuous measurement of local absolute CBF. This technique is based on thermal conductivity of brain tissue: the temperature difference between the neutral plate and the heated element reflects local CBF [64]. Validation studies show that TD regional CBF values agree with regional CBF values obtained using xenon-enhanced CT studies or the hydrogen clearance method [65, 66]. TD probes can be placed on the brain surface during a craniotomy, e.g., the Flowtronics probe (Flowtronics, Phoenix, AZ, USA), or the probe may be positioned through a burr hole and secured with a metal bolt in the brain parenchyma (e.g., Hemedex, Cambridge, MA, USA).

The Hemedex probe can be easily inserted while the patient is in the ICU. Its tip lies about 25 mm below the dura, where it measures subcortical white matter perfusion. A CT scan should be performed to verify its position. A mean TD value of 18–25 ml/100 g/min is considered normal [65, 66]; however, serial changes or trends rather than absolute values may better detect early neurological deterioration or vasospasm or help assess a response to therapy [67]. In TBI, TD flowmetry can also be used to guide adequate perfusion or identify “optimal” CPP. In addition TD regional CBF values are associated with outcome. Patients with a significant regional CBF increase from the baseline tend to have a good outcome, whereas initial very low values when there is no increase from the baseline are associated with a poor outcome [68, 69].

TD flowmetry has several limitations: (1) it is invasive and so there are rare risks of bleeding and/or infection; (2) it provides only a single focal CBF measurement from a small brain volume; (3) fever, loss of tissue contact, or position near large vessels may reduce accuracy or reliability [64, 70]; (4) automatic recalibration occurs every 30 min, during which time data are briefly lost (2–5 min); and (5) measurements are prevented for safety reasons when the temperature is greater than 39 °C and so data may be lost.

Laser Doppler Flowmetry

There are several main manufacturers of LDF instruments, e.g., Perimed (Stockholm, Sweden), Moor Instruments (Axminster, UK), Vasamedics (St Paul, MN, USA), Transonic Systems (Ithaca, NY, USA), Oxford Optronix (Oxford, UK), and LEA Medizintechnik (Giessen, Germany). In this technique, a small fiber-optic laser probe (diameter 0.5–1 mm) applied in or on the brain is used to illuminate a 1-mm³ tissue volume with monochromatic laser light of wavelength between 670 and 810 nm. When the light strikes the tissue, photons are scattered and Doppler shifted in a random fashion by stationary tissue or moving red blood cells. These photons are detected by photoreceptors that generate an electric signal proportional to the volume and velocity of red blood cells according to Bonner and Nossal's algorithm [71]. LDF perfusion is expressed in arbitrary units [71, 72] since LDF measures erythrocyte flux rather than actual CBF [73–76]. However, LDF values correlate well with measures of CBF, e.g., xenon clearance method, radioactive microspheres, hydrogen clearance technique, iodoantipyrine method, and TD flowmetry [77, 78].

In TBI patients, LDF can provide continuous, bedside measurements of microvascular perfusion. Although LDF data are qualitative and regional [79], these monitors have excellent temporal and dynamic resolution with ultrashort time responses to regional CBF fluctuations. This can be used to assess autoregulation and CO₂ reactivity, detect

ischemic insults, or evaluate therapeutic responses [80, 81]. In addition, LDF data are associated with outcome: preserved autoregulation determined with LDF [82] and greater LDF readings during a transient hyperemic response are associated with better outcomes [83].

There are several limitations to LDF use. First, LDF is an invasive technique. Second, it measures CBF in a small brain volume in a semiquantitative manner and so LDF monitors are best used as trend monitors. Third, external factors, e.g., room temperature, strong external light, and sound, or internal factors, e.g., microvascular heterogeneity, changes in hematocrit, and tissue or probe motion, may influence accuracy. Finally, LDF probes require frequent calibrations.

Brain Oxygen

Monitoring of cerebral oxygenation after TBI can help guide therapy, calculate optimal ICP or CPP in individual patients, identify episodes of secondary brain injury before irreversible damage occurs, and inform prognosis [31••]. There are four broad methods to measure brain oxygenation: jugular venous bulb oximetry, direct brain tissue oxygen tension measurement, NIRS, and oxygen-15 PET. A discussion on PET, an imaging study, is beyond the scope of this review. The interested reader is referred elsewhere [84, 85•, 86, 87].

Jugular Venous Bulb Oximetry

The jugular bulb is the final common pathway for venous blood that drains the brain, and oxygen saturation at the jugular bulb ($S_{jv}O_2$) indicates the balance between supply and oxygen consumption by the brain. Therefore, a catheter placed in the jugular bulb allows assessment of global brain oxygenation when the dominant jugular bulb is cannulated [88]. Often the jugular foramen size on CT will be larger for the dominant jugular vein. In addition, facial vein contamination must be avoided for accurate measurement. Catheter position should be confirmed on X-ray (lateral skull or cervical spine); it should be at the level of and just medial to the mastoid bone above the lower C1 border.

$S_{jv}O_2$ can be measured continuously through a fiber-optic oximetric catheter, e.g., Oximetrix (Abbott Laboratories, North Chicago, IL, USA) or Edslab II (Baxter Healthcare, Irvine, CA, USA). Intermittent sampling is cheaper and permits calculation of arteriovenous difference in oxygen content ($AVDO_2$), glucose, and lactate on the basis of the Fick principle [89]. When the cerebral metabolic rate is stable, $AVDO_2$ changes indicate CBF changes and so provide information about the adequacy of CBF [90]. However jugular bulb catheters do not provide quantitative or regional CBF measurements [91]. The cerebral

metabolic rate for oxygen ($CMRO_2$) can be calculated when CBF and $AVDO_2$ are known:

$$CMRO_2 = CBF \times (\text{arterial oxygen content} - \text{jugular venous bulb oxygen content}).$$

$AVDO_2$ and $S_{jv}O_2$ can be used to relate changes in $CMRO_2$ with CBF. Ischemia is associated with increased $AVDO_2$, whereas hyperemia leads to a reduced $AVDO_2$. The same principle applies to other metabolites, e.g., glucose and lactate. Normal $S_{jv}O_2$ is between 55 and 75 %. Reduced $S_{jv}O_2$ indicates increased oxygen demand, e.g., fever or seizures or reduced oxygen delivery, e.g., vasospasm or inadequate CPP. The ischemic threshold is an $S_{jv}O_2$ of less than 50 % for at least 10 min [92]. However, PET studies suggest that a relatively large brain volume (approximately 13 %) must be affected before $S_{jv}O_2$ levels decrease below 50 % [74, 93]. Increased $S_{jv}O_2$ (above 70 %) suggests that CBF is greater than the brain needs (hyperemia) or decreased metabolic demand.

Episodes of $S_{jv}O_2$ desaturation are common in comatose TBI patients despite ICU care [94, 95] and these desaturations (particularly $S_{jv}O_2$ less than 50 % for more than 15 min) are associated with poor neurological outcome in TBI [95]. When used with other monitors, jugular bulb catheters can help define treatment thresholds, e.g., titrate hyperventilation in patients with increased ICP [96]. There are several potential limitations associated with jugular bulb catheters. First, sensitivity is low [74, 93]. Second, heterogeneity in CBF or metabolic rate may result in misleading information, e.g., when hyperemic areas overshadow focally ischemic areas. Third, changes in arterial oxygen content, hemodilution, or jugular bulb catheter position, frequent calibrations, or an ICP increase can affect reliability. Finally, between 1 and 4 % of insertions are associated with complications such as arterial puncture, venous air embolism, venous thrombosis [97], pneumothorax, or damage to adjacent structures, e.g., vagus and phrenic nerves, or the thoracic duct. Long-term use is associated with local and systemic infection.

Direct $PbtO_2$ Measurement

Brain oxygen ($PbtO_2$) monitors were first used in the clinical environment in 1993 and were included in the treatment guidelines for severe TBI in 2007 [98]. Two techniques are available: (1) a modified Clark electrode that uses the electrochemical properties of noble metals, e.g., Licox (Integra Neuroscience, Plainsboro, NJ, USA) and Neurovent-P Temp[®] (Raumedic, Münchberg, Germany) and (2) the optical fluorescence technology Neurotrend (Diametrics Medical, St Paul, MN, USA) and OxyLab pO_2 [®] (Oxford Optronix, Oxford, UK).

The Licox probe has been most frequently used in ICU practice. It is based on the Clark principle, which is temperature-dependent, and so a temperature probe is supplied with the PbtO₂ probe. Direct PbtO₂ monitors provide a measure of PbtO₂ in units of tension (mmHg). A conversion factor of 1 mmHg=0.003 ml O₂/100 g brain can be used to convert PbtO₂ values to units of concentration (ml O₂/100 ml). A PbtO₂ monitor is not a blood flow monitor. Instead, it indicates the balance between regional oxygen supply and cellular oxygen consumption and may be described by the equation: PbtO₂ = CBF×AVTO₂, i.e., the interaction between plasma oxygen tension and CBF [99]. PbtO₂ is influenced by many factors, including CBF and the factors that regulate it, e.g., CO₂ and MABP, but also with changes in arterial oxygen tension and so lung function and hemoglobin concentration [99–103]. In addition, a PbtO₂ monitor is different from a jugular bulb catheter that measures the venous oxygen content in blood leaving the brain, i.e., the balance between oxygen delivery and oxygen use. By contrast, PbtO₂ is consistent with the oxygen that accumulates in brain tissue, and PET studies suggest it may correlate inversely with the oxygen extraction fraction [86] and reflect oxygen diffusion rather than total oxygen delivery or metabolism [29, 102, 104].

PbtO₂ threshold values depend on what type of monitor is used. In general when using a Licox monitor, PbtO₂>25–30 mmHg is considered normal [105, 106]; values below 20 mmHg are considered worth treating, and values below 15 mmHg are consistent with brain hypoxia or ischemia (Table 4) [103, 106–111]. The number, duration, and intensity of episodes of PbtO₂ <15 mmHg, and any PbtO₂ values of 5 mmHg or less are associated with poor outcome after TBI [108–114]. Indeed PbtO₂ <10 mmHg is associated with a twofold to fourfold increase in both mortality and unfavorable outcome [32]. However, the exact relationship between PbtO₂ and outcome varies with probe location: e.g., in normal white matter, the penumbra, or in a contusion [104, 115•]. Consequently, like all other monitors, the information provided by a PbtO₂ monitor should be interpreted with data from other monitors, e.g., an ICP monitor and CT scan findings.

In microdialysis studies, decreases in PbtO₂ are associated with markers of cellular dysfunction [116]; hence, PbtO₂ monitoring is useful in clinical conditions where cerebral

ischemia or secondary brain injury may occur [86, 117]. In TBI, PbtO₂ monitors may be an ideal complement to ICP monitors, since compromised PbtO₂ or episodes of brain hypoxia are common and can occur even when ICP and CPP are normal [28, 118]. Use of PbtO₂ and ICP (or other) monitors together improves insight about the complex pathophysiology of the brain after TBI, and allow ICU staff to examine autoregulation and identify optimal physiological targets, including CPP, hemoglobin concentration, and temperature or the need for or effects of therapies, e.g., hyperventilation, induced hypothermia or hypertension, transfusion, hypertonic saline, and decompressive [57, 119–125]. When severe TBI care is based on both PbtO₂ and ICP, some but not all observational series suggest outcome is better than when just ICP-based care is provided [126–128, 129•]; this question is now being evaluated in a multicenter clinical trial.

Near-Infrared Spectroscopy

NIRS is a noninvasive technique that measures regional cerebral oxygen saturation (rSO₂). This technique relies on the concept that light of wavelengths between 680 and 1,000 nm is able to penetrate human tissue and is absorbed by the chromophores oxyhemoglobin, deoxyhemoglobin, and cytochrome oxidase. The amount absorbed depends on tissue oxygenation or metabolism. Today, commercially available monitors, e.g., INVOS cerebral oximeter (Somanetics, Troy, MI, USA) and the Hamamatsu 100, 200, and 300 oxygenation monitors (Hamamatsu Photonics, Japan), are portable and provide bedside noninvasive measurements of cerebral oxygenation. The values obtained are closely related to cerebral venous oxygen saturation; rSO₂ values between 60 and 80 % are considered as the normal range [130].

In the adult, most NIRS systems are placed in the fronto-temporal region. Many factors can influence cerebral rSO₂, including ambient light, hair follicles, the volume and type of tissue being illuminated, and signal contamination by the extracranial tissue layers [131]. The accuracy of cerebral rSO₂ as a quantitative measure, normal values, and NIRS-derived “thresholds” for ischemia/hypoxia have still to be established [132]. In addition, NIRS does not resolve focal CBF abnormalities but may be useful as a monitor of general changes and trends over time. For these reasons, NIRS has yet to be validated for routine use in TBI although there are several studies that suggest a role of NIRS in the evaluation of a low cardiac output state [133], noninvasive CAR assessment [134], and in TBI patients [135–137].

Cerebral Metabolism

Brain metabolism can be assessed at the bedside using CMD, which allows low molecular weight substances from

Table 4 Licox partial pressure of brain tissue O₂ (PbtO₂) values (from [32, 98, 103, 105, 106, 111, 112, 116])

PbtO ₂ value (mmHg)	State
25–35	Normal
20	Compromised (begin treating)
15	Brain hypoxia
10	Severe brain hypoxia
5	Cell death

the interstitial space (i.e., brain extracellular fluid) to be collected and sampled through a specialized catheter with a semipermeable dialysis membrane at its tip that is placed in the brain parenchyma. In clinical use, the CMD catheter, usually with a cutoff of 20 kDa, is constantly perfused with a CSF-like solution. This allows regular (usually each hour) sampling of the patient's brain extracellular fluid through a bedside analyzer. In TBI, the most commonly examined analytes are markers of cerebral energy metabolism (glucose, lactate, and pyruvate), neurotransmitters (glutamate), and cell damage (glycerol). Threshold values for various CMD markers are described (Table 5). However, there is variation among patients and so trend interpretation is more useful than absolute measures. Importantly, changes in microdialysis analytes can precede changes in other physiological variables, e.g., ICP [138, 139].

Measurements of glucose, pyruvate, and lactate provide information about brain bioenergetics. CMD glucose levels are reduced in patients with severe TBI and consistently low concentrations (less than 0.66 mmol/l) are associated with poor outcome [140]. Reduced glucose levels can result from reduced supply (decreased perfusion) or hyperglycolysis [141]. Lactate and pyruvate concentrations provide further information about the relative contributions of aerobic and anaerobic metabolism. The lactate-to-pyruvate ratio (LPR) reflects the cytoplasmic redox state and is the most commonly examined CMD marker measured after TBI. An increased LPR (greater than 40) can indicate cerebral hypoxia or ischemia [142]. There also are several potential nonhypoxic/ischemic causes of an increased LPR [143•]; whether the level of pyruvate increases or decreases can help differentiate ischemic from nonischemic reasons for an elevated LPR. There is well-described association between elevated LPR and poor outcome after TBI [144–146, 147••].

Glycerol and glutamate are less commonly assayed substances. Glycerol levels increase with membrane breakdown, and increased glycerol is associated with unfavorable outcome after TBI [148]. However, an increase in glycerol concentration may also be observed when there is blood–brain barrier breakdown, and so CMD glycerol levels need cautious interpretation unless

there is an abdominal subcutaneous catheter as well since this may help indicate the status of the blood–brain barrier. Increased CMD glutamate concentration is observed in TBI patients with poor outcome [144, 145, 149]. However, glutamate concentration is now less frequently measured since the relationship between glutamate and outcome is more complex than first thought [150, 151].

CMD is labor-intensive and presently it is largely a research tool. However, its use has increased our understanding of the pathophysiology of TBI. In addition, CMD has been used to identify optimal physiological targets, including CPP, hemoglobin concentration, and temperature and the effects of various therapies, including glycemic control, hyperventilation, induced normothermia, and surgery [49, 122, 152–155]. The role of CMD is described in several excellent reviews and a consensus statement about its use [142, 156, 157].

Electrophysiological Measurements

Electroencephalography

The electroencephalogram has been used for many years to noninvasively examine the electrical activity of the cerebral cortex. In particular EEG is used for seizure detection and to help manage seizures and status epilepticus. In critically ill patients, seizures can frequently be nonconvulsive and not easy to detect by clinical means [158]. These nonconvulsive seizures may occur in up to 40 % of severely injured patients and can exacerbate brain injury [159]. Quantitative EEG, in which the raw EEG signal is converted into a digital form using fast Fourier transformation (compressed spectral array), has evolved in the last decade. This and recent advances in computer technology have made continuous EEG monitoring practical and EEG interpretation easier in the ICU. This is important since traditional intermittent EEG is less sensitive than continuous EEG to detect nonconvulsive seizures or status epilepticus [160, 161].

Since neuronal activity and CBF are coupled, continuous EEG can also be used to detect new or worsening brain ischemia. EEG changes occur within seconds of CBF reduction [162, 163]; the observed change depends on the extent of CBF decrease (Table 6). Therefore, EEG can detect a time period when intervention may prevent irreversible injury. Quantitative and continuous EEG is particularly useful for this purpose in the ICU and has been best studied in SAH, where trend analysis of total power (1–30 Hz), variability of relative alpha (6–14 Hz/1–20 Hz), and post-stimulation alpha/delta ratio (8–13 Hz/1–4 Hz) [164–166] are associated with cerebral ischemia or angiographic vasospasm. In addition, these variables are associated with outcome after SAH and TBI.

Table 5 Cerebral microdialysis thresholds (modified from [185, 186])

	Threshold		
	Reinstrup et al. [185]	Schulz et al. [186]	Clinical use
Glucose (mmol/l)	1.7 (±0.9)	2.1 (±0.2)	<2.0
LPR	23 (±4)	19 (±2)	>25
Glycerol (μmol/l)	82 (±44)	82 (±12)	>100
Glutamate (μmol/l)	16 (±16)	14 (±3.3)	>15

LPR lactate-to-pyruvate ratio

Use of EEG in the NCCU requires close collaboration between several disciplines. In addition, training staff to differentiate epileptiform patterns from artifacts is essential. Continuous EEG has many characteristics of an ideal physiological monitor in the ICU (Table 1). However, there are several technical (e.g., digital analysis and data reduction or electrical artifacts associated with a noisy NICU environment), patient-related (constant fixation of electrodes for patients who are agitated or who require transport; altered cranial anatomy such as monitoring devices, ventricular catheters, skull defects, or scalp edema), or system resource (e.g., availability of 24-h coverage of experienced electroencephalographers, availability of networking with real-time and event-response access; automated alerting systems; and accessibility of remote online analysis resource) factors that can potentially limit the use of continuous EEG for immediate clinical decision-making in all patients [167]. EEG is also a “backend” monitor, i.e., it provides information on function. It is therefore best used with other monitors since they may show a pathophysiological change before the functional change.

Evoked Potentials

Somatosensory evoked potentials (SSEPs) are measured on the scalp as evoked EEG responses to an electrical stimulus typically applied to the median or tibial nerves. Pharmacological agents or hypothermia affect SSEPs less than EEG. SSEPs have primarily been used to indicate the severity of injury or prognosis and are best studied in cardiac arrest. The main variable used for prognosis is the cortical response or N20 peak that typically occurs 20–ms after the stimulus. After cardiac arrest, bilateral absence of the N20 SSEP is associated with persistent vegetative state or death [168, 169]. The role of evoked potentials in TBI patients is less certain but can provide helpful information about prognosis in some patients.

Biomarkers

In 2001, an NIH working group standardized the definition of a biomarker as “a characteristic that is objectively measured

Table 6 EEG changes and detection of cerebral ischemia

CBF (ml/100 g/min)	EEG change	Reversibility
35–70	Normal	No injury
25–35	Loss of beta	Reversible
18–25	Theta slowing	Reversible
12–18	Delta slowing	Reversible
< 8–10	Suppression	Irreversible

and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” There are three broad types of biomarkers: (1) measured on a biosample (e.g., blood, urine, CSF, or tissue test), (2) a recording obtained from a person (e.g., blood pressure, ECG), or (3) an imaging study (e.g., MRI or CT scan). Recent parallel developments have revolutionized the biomarker field. First, the completion of the Human Genome Project and the development of microarrays, proteomics, and nanotechnology have provided new methods to develop sensitive high-throughput assays. Second, advances in bioinformatics and cross-disciplinary collaborations have enhanced the ability to retrieve and analyze large amounts of data. Third, there is increased recognition that diseases arise out of the dynamic dysregulation of several gene regulatory networks, proteins, and metabolic alterations, reflecting complex perturbations (genetic and environmental) of the “system.”

In daily practice neurointensivists focus on the recognition of subtle changes in the neurological condition, interactions between the brain and systemic derangements, and brain physiology. The challenge for intensivists is to identify individuals who are at risk of developing disease or secondary injury, determine disease severity, and distinguish the responders to therapy from the nonresponders to therapy (i.e., individualized and targeted medicine). Biomarkers are one tool that can answer these challenges since they can act as antecedent (preclinical), screening, diagnostic, staging, or prognostic disease markers. Furthermore, biomarkers can be used to monitor treatment efficacy and as surrogate end points in clinical trials. For example, advances in cardiology and AIDS research have led to use of early (mechanistic) end points, i.e., troponin in myocardial infarction and CD4 counts in AIDS.

A variety of biomarkers (biosamples; Table 7) have been examined in TBI, and although promising results are available, the ideal brain marker (the troponin of the brain) does not yet exist. Brain biomarkers are categorized according to their

Table 7 Some examples of biomarkers (biosamples from serum or CSF) of brain injury

Tissue-specific
Neurons (neuron-specific enolase, tau)
Glia (S100β, glial fibrillary protein, myelin basic protein)
Mechanism-specific
Proteases (calpain and caspase cleavage products)
Oxidative stress (isoprostanes, nitrotyrosine)
Inflammation (s-ICAM, IL-6, IL-8)
Disease-specific
Creutzfeldt–Jakob disease (14.3.3 protein)
Alzheimer’s disease (tau/Aβ42)

s-ICAM soluble intercellular adhesion molecule

source as primarily neuronal, astroglial, or microglial; most biosample research has concentrated on single-marker assays, e.g., S100 β , glial fibrillary acidic protein (GFAP), neuron-specific enolase, tau, neurofilament heavy chain, and α II-spectrin. There is a significant body of research on S100 β , an astroglial protein that is found in serum and CSF after TBI. Increased levels of S100 β are associated with injury severity and poor outcome [170], but although sensitive, the specificity of this marker for acute brain injury is poor [171]. Another astroglial protein is GFAP, increased serum levels of which are observed in TBI [172, 173]. GFAP may be better able to discriminate TBI outcomes than S100 β [173]. Neuron-specific enolase is an enzyme found in neurons, erythrocytes, and platelets. It is better studied in cardiac arrest than in TBI, but increased levels are observed after TBI and appear to be associated with outcome. Tau and neurofilament heavy chain are other neuronal proteins associated with the cytoskeleton. Increased levels can be found in CSF or using CMD, i.e., brain interstitial fluid after severe TBI [174, 175, 176]. Serum levels, however, are not reliable. Finally, another component of the neuronal cytoskeleton, α II-spectrin, is degraded after TBI. The concentrations of the spectrin breakdown products are increased in CSF after TBI and are associated with injury severity and 6-month outcome [177]. Despite much research, single-marker biosamples have yet to enter routine use in the NCCU. However, an emerging body of work suggests that multimarker panels may enhance sensitivity and specificity for acute neurological injury [178, 179, 180]. Biomarkers are likely to play an increasing role in TBI management soon.

Informatics and the Future of Monitoring

Critical care management of TBI is centered on the identification, prevention, and management of secondary cerebral insults. This depends on monitoring, the goals of which are summarized in Table 8. In large part today, neuromonitoring is based on a “reactive” model, in which an abnormal value of a single parameter triggers corrective action(s) to reverse the

Table 8 Why do we monitor?

To detect early neurological worsening before irreversible brain damage occurs
To individualize patient care decisions
To guide patient management
To monitor therapeutic response of some interventions and to avoid any potential adverse effects
To allow clinicians to better understand the pathophysiology of complex disorders
To design and implement management protocols
To improve neurological outcome and quality of life in survivors of severe brain injuries

Table 9 Requirements for multimodality monitoring in traumatic brain injury care (modified from [181, 183, 184])

Continuous monitoring
Not to miss clinically significant events
The frequency of monitoring needs to be higher than the duration of the events to be detected
Comprehensive
All of the necessary data for a particular monitoring goal need to be collected simultaneously, time-synchronized, and displayed in an integrated fashion
Communicative
Plot time synchronized trends on a single display
Integrate waveforms, images, and other formats
Statistical relationships

process. This management strategy is generally threshold-based rather than trend-based and uses a stepwise approach with an increasing therapy intensity that is often phenomenological rather than mechanistic, i.e., it may be separate from the underlying pathophysiological condition. In addition, the brain (and its function) is complex and different pathophysiological processes may occur in TBI patients simultaneously or sequentially, and to differing degrees. Therefore, a one size fits all reactive therapy based on individual parameters, i.e., a single monitor, is an oversimplified approach to TBI care

There are many techniques that can be used to assess brain function after TBI, both directly and indirectly. A combination of monitoring techniques that can provide real-time information about the relative health or distress of the brain is ideal, i.e., multimodality monitoring. Multimodality monitoring is the digital simultaneous recording of multiple parameters of brain function [181]; requirements for multimodality monitoring are listed in Table 9. This then allows “individualized therapeutic strategies” based on our

Table 10 Challenges to neurocritical care unit informatics (modified from [184])

Data acquisition electronically as a standard in intensive care units
Interoperability of different monitoring devices to acquire data
Standardization of global controlled vocabularies of terminology
Volume and resolution of data
Regulatory aspects of data collection (e.g., HIPAA and privacy boards)
Automated artifact detection and cleaning of acquired data before analysis
Missing data due to artifact, disconnection, different time domains, etc.
Differing types of data (e.g., numeric, imaging, text, continuous, ordinal)
Integration with electronic medical records and other patient data
Whether to use all data or discard data selectively or empirically
Real-time analysis and feedback to the bedside
Clinician acceptance and use of analyzed data

HIPAA Health Insurance Portability and Accountability Act

understanding of what is going on in the brain. In addition, rather than simply using data from the monitors to indicate when critical deviations occur, one should ideally use the data to guide goal-directed therapy through an integration of real-time physiological end points (which are often more important than single values) before the critical threshold is reached. Presently the multimodality monitoring concept is still relatively primitive but is rapidly evolving as the field of bioinformatics advances. Some systems are available now, e.g., ICM + and ICU Pilot. Collaborative projects such as BrainIt [182] demonstrate that the recording of many physiological variables across multiple patients is feasible and leads to new clinical insights [147•, 183]. However, most of the advanced statistical and mathematical tools currently are applied post hoc to a large volume of data from multiple patients. Although this provides information about patterns of brain injury and easier identification of specific targets, including new targets, considerable efforts (Table 10) still are needed to advance the multimodality monitoring concept into routine NCCU use to provide real-time, synchronized, user-friendly advanced data analysis for the individual patient [184•]. Not all NCCUs (and those working in them) are ready to use multimodality monitoring, and educational initiatives are needed since the concept is a paradigm shift and will change the way in which TBI patients are monitored and treated. In particular, multimodality monitoring may allow us to differentiate between pathological conditions that appear similar, but require different treatments [1•].

Conclusion

In this article we have reviewed physiological monitoring techniques of brain function used during the intensive care management of TBI patients. A variety of regional and global monitors are available that are perhaps best used in combination and interpreted with clinical and imaging findings. Some of the techniques are well established, whereas others are new to ICU care and their indications for use and how to incorporate the information into patient care are still being evaluated. However, multimodality monitoring can help us to understand what is going on in the brain of a given patient at a particular moment. This provides a direct link towards individualized targeted treatment that has the potential to be more mechanistic than empiric in nature. Importantly, it is not the monitoring that makes a difference, but how the information provided is translated into patient care.

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