CRITICAL CARE

REVIEW

Clinical review: Neuromonitoring - an update

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Abstract

Critically ill patients are frequently at risk of neurological dysfunction as a result of primary neurological conditions or secondary insults. Determining which aspects of brain function are affected and how best to manage the neurological dysfunction can often be difficult and is complicated by the limited information that can be gained from clinical examination in such patients and the effects of therapies, notably sedation, on neurological function. Methods to measure and monitor brain function have evolved considerably in recent years and now play an important role in the evaluation and management of patients with brain injury. Importantly, no single technique is ideal for all patients and different variables will need to be monitored in different patients; in many patients, a combination of monitoring techniques will be needed. Although clinical studies support the physiologic feasibility and biologic plausibility of management based on information from various monitors, data supporting this concept from randomized trials are still required.

Introduction

The overall aims of neuromonitoring are to: 1) identify worsening neurological function and secondary cerebral insults that may benefit from specific treatment(s); 2) improve pathophysiological understanding of cerebral disease in critical illness; 3) provide clear physiological data to guide and individualize therapy; 4) assist with prognostication. In this article, we will outline the neuromonitoring techniques currently in use in critically ill patients and suggest how they should be best applied to help us care for such patients. We will focus on clinically available techniques and not discuss new approaches that are still largely in the research stage of development.

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Pathophysiology of acute brain injury

The pathophysiology of acute brain injury is complex and can involve several secondary pathological cascades that contribute to aggravate neuronal injury (Figure 1). The clinical rationale for neuromonitoring is to tailor therapy to patient-specific pathophysiology rather than to predefined thresholds or targets. It is thus important to briefly review some basic aspects of brain physiology to help understand the techniques and applications of neuromonitoring.

Cerebral metabolism

The human brain constitutes 2% of body weight, yet the energy-consuming processes that enable adequate brain function account for about 25% of total body energy expenditure and 20% of the oxygen consumption of the whole organism. Glucose is the main energy substrate of the brain and, given the low glycogen stores in the brain, brain glucose levels are highly dependent on blood glucose. Transport of glucose from the systemic circulation to the brain is a tightly regulated process mediated by specialized cell membrane glucose transporters (GLUT). Experimental and human studies show evidence of flow-metabolism uncoupling and increased glucose utilization after acute brain injury ('cerebral hyperglycolysis'). Importantly, this can occur in the absence of low cerebral blood flow (CBF) and cerebral ischemia and may lead to a state of reduced availability of the main energy substrate (glucose) with a subsequent risk of cerebral energy dysfunction [1,2]. However, hyperglycolysis also results in increased processing of glucose to pyruvate by astrocytes and conversion to lactate. Endogenous lactate, released in the extracellular space, can in turn be transferred, via specific monocarboxylate transporters, to neurons (a process known as the 'astrocyte-neuron lactate shuttle') [3]. Brain lactate may thus be used as an alternative aerobic energy substrate to glucose [4]. Indeed, studies in subarachnoid hemorrhage (SAH) patients suggest that a pattern of increased cerebral hyperglycolytic lactate is associated with better outcome [5].

Cerebral blood flow, oxygen delivery and ischemia

Cerebral ischemia is a frequent cause of secondary brain injury [6]. In normal conditions, reduced systemic

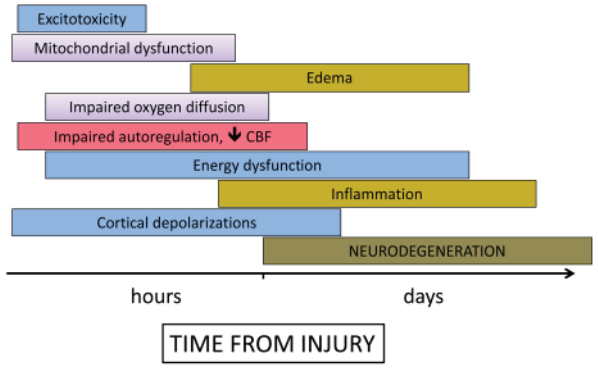

Figure 1. Some of the pathological cascades contributing to aggravate neuronal injury after acute brain injury. Initial mechanisms, such as excitotoxicity and mitochondrial dysfunction, initiate damage in the very early minutes/hours; other factors, such as energy dysfunction, edema, and inflammation come into play later in the process. CBF, cerebral blood flow.

pressure triggers an active vasodilatory response that keeps cerebral blood flow (CBF) constant over a wide range of mean arterial pressures (MAPs), thereby preventing brain hypoperfusion (cerebral pressure autoregulation) [7]. In brain-injured patients, cerebrovascular reactivity may be impaired, and a decrease in MAP or cerebral perfusion pressure (CPP) may thus translate into reduced CBF and secondary ischemia [8].

Cerebral oxygen utilization is proportional to the product of CBF and the arterio-venous difference in oxygen content [9]. Mechanisms other than perfusion-limited ischemia (microvascular collapse, endothelial swelling, perivascular edema) may increase the diffusion gradient for oxygen between venous blood and brain tissue (PvO_2-$PbtO_2$), reduce cellular oxygen delivery and attenuate the ability of the brain to increase oxygen extraction fraction in response to reduced CBF [10].

Neurological examination of the ICU patient

Clinical neurological examination is a fundamental component of neuromonitoring and should take into account the effects of sedative drugs, which may markedly influence neurological responses. The degree of awareness should first be assessed. Clinical assessment is based mainly on evaluating eye and motor responses to verbal orders and noxious stimuli. The depth of coma can be evaluated by the Glasgow Coma Scale (GCS) [11] or the Full Outline of UnResponsiveness (FOUR) score [12], which includes assessment of the pupillary light and corneal reflexes and of the breathing pattern. Delirium is a fluctuating state characterized by altered attention, spatio-temporal disorientation, disorganized thinking and alteration of awareness. Delirious patients can be hypoactive, hyperactive or both alternately. The Confusion Assessment Method for the ICU (CAM-ICU) [13] or the ICU Delirium Screening Checklist (ICU DSC) [14] can be used to assess the presence and degree of delirium.

Neurological examination should then assess for neck stiffness, motor responses, plantar and deep tendon reflexes and cranial nerve functions. The presence of focal neurological signs should prompt brain imaging, which should also be considered, along with an electroencephalogram (EEG), if there is no obvious cause for delirium or coma.

Monitoring techniques

Intracranial pressure

Elevated intracranial pressure (ICP; >20 mmHg) is associated with increased mortality after acute traumatic brain injury (TBI) [15]. The most recent Brain Trauma Foundation guidelines [16] recommend (level II evidence) that ICP should be monitored in all salvageable patients with severe TBI (GCS score of 3 to 8 after resuscitation) and an abnormal head CT scan.

ICP monitoring is also used in non-traumatic neurological disorders, such as SAH, and to a lesser extent in brain tumors, infarctions, intracerebral hemorrhage, and infections. After SAH, external ventricular drainage is recommended in patients with higher World Federation of Neurological Societies (WFNS) scale scores or acute hydrocephalus [17], to monitor ICP and to drain cerebrospinal fluid (CSF) for ICP control. In spontaneous intracerebral hemorrhage, ICP monitoring is seldom used, but recent guidelines [18] suggest that in patients with a GCS score of <8, those with clinical evidence of transtentorial herniation, or those with intraventricular hemorrhage or hydrocephalus, ICP monitoring and treatment may be considered (class IIb; level of evidence: C).

ICP is a function of intracranial content: some content is easy to detect and correct, such as an expanding contusion, while others are more difficult - for example, in cases of diffuse cerebral swelling, which may indicate vasodilation or edema. The volume-pressure curve, which describes ICP changes to corresponding increases in volume, has an exponential shape: as long as compensatory mechanisms can be used (that is, displacement of CSF from the supratentorial space into the spinal sac), ICP will remain constant despite the volume increase. When compensatory capabilities are exceeded, ICP rises sharply. Attempts have been made to identify loss of compensation using ICP waveform analysis: the normal ICP waveform has three components (P1 > P2 > P3), but is altered when pressure increases, with an increase in the P2 component compared to P1 (Figure 2); the ICP pulse amplitude (difference between systolic and diastolic values) also tends to increase [19]. However, this feature depends on the CPP and on the physical properties of the measuring system, and so should be used with caution.

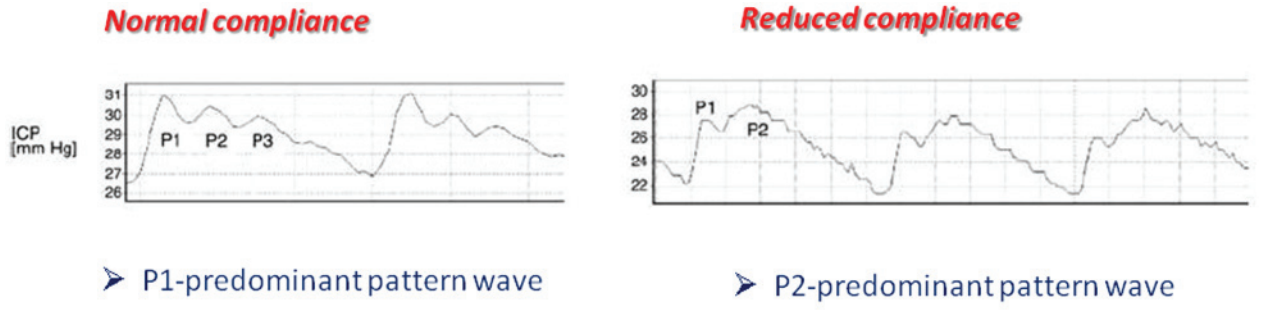

Figure 2. Intracranial pressure curve in conditions of normal and reduced compliance. Valuable information on intracranial buffering mechanisms can be extracted from the shape of the curves: when all normal components (peaks) of the intracranial pressure (ICP) curve are clearly evident (left panel), the intracranial system is behaving normally and small increases in volume can still be compensated for. However, when a P2-predominant pattern is displayed (right panel), the intracranial system is less compliant and compensatory abilities are reduced.

Although non-invasive evaluation of ICP is possible using the transcranial Doppler (TCD)-derived pulsatility index [20] or optic nerve sonography [21], the only methods for continuous on-line monitoring of ICP remain invasive. Intra-ventricular devices have long been considered the 'gold standard'; however, intra-parenchymal pressure monitoring provides equivalent pressure measurements [22]. Intraventricular probes are particularly useful when CSF drainage is desirable.

ICP management should also take CPP into account (Figure 3). Therapies to reduce intracranial hypertension that also may reduce arterial pressure and CPP (for example, barbiturates) require careful titration to preserve adequate cerebral perfusion.

Cerebral blood flow

Direct, continuous measurement of regional CBF is now feasible using a thermal diffusion probe (TDP; Hemedex® Cambridge, Massachusetts, USA) inserted into the brain parenchyma. The sensor at the tip provides a quantitative measure in the volume of tissue surrounding the sensor. The TDP technique showed good agreement with CBF measured by xenon-CT [23].

Correct and stable positioning of regional CBF probes with a skull bolt is crucial and a CT-scan should be performed to verify correct placement. Precise quantification of regional CBF using a TDP is dependent on the presence of a stable temperature and may be altered in conditions of hyperthermia or rapid fluctuation in a patient's temperature.

In patients with SAH, Muench and colleagues [24] used TDP monitoring to guide medical therapy for delayed cerebral ischemia, and demonstrated that increasing blood pressure with vasopressors was the only intervention that improved CBF and $PbtO_2$; hypervolemia and hemodilution had only marginal effects at best. Hence, normovolemia and MAP/CPP augmentation are increasingly used instead of 'triple-H' therapy in these patients. TDP monitoring may also guide CPP management after TBI [25]. TDP data are currently limited to small single-center studies and larger trials are needed to confirm the validity and use of this technique.

Transcranial Doppler

Direct measurement of blood flow in the brain arteries would be of value in all cases of brain damage. Using an ultrasound probe, flow velocity (rather than flow itself) can be measured in the main arteries of the base of the brain. TCD combines ultrasound and the Doppler principle to represent erythrocyte flow in the basal cerebral arteries. In some 10% of patients, transtemporal insonation is not feasible because of anatomical barriers. When cerebrovascular resistance increases - for example, in vasospasm of the middle cerebral artery - systolic TCD velocity increases, whereas diastolic velocity decreases, leading to a clear increase in the pulsatility index (the ratio of the difference between systolic and diastolic flow to diastolic flow). For this reason, TCD is often used to monitor the time course of vasospasm after SAH [26]. However, correct interpretation of the pulsatility index is complex, because it depends not only on cerebrovascular resistance, but also on several systemic and cerebral variables [27].

TCD has also been used to assess cerebrovascular autoregulation in TBI and SAH patients [7]. Flow velocity responses to spontaneous or induced (with vasopressors) changes in CPP may quantify the status of static pressure autoregulation; autoregulation estimated by TCD in the middle cerebral artery correlated with autoregulation studied by positron emission tomography in TBI patients [28].

The main advantage of TCD is that it is non-invasive and can be carried out at the bedside. However, the quality of the TCD signal is operator-dependent and correct interpretation requires training. TCD signals may also vary over time with temperature, arterial carbon

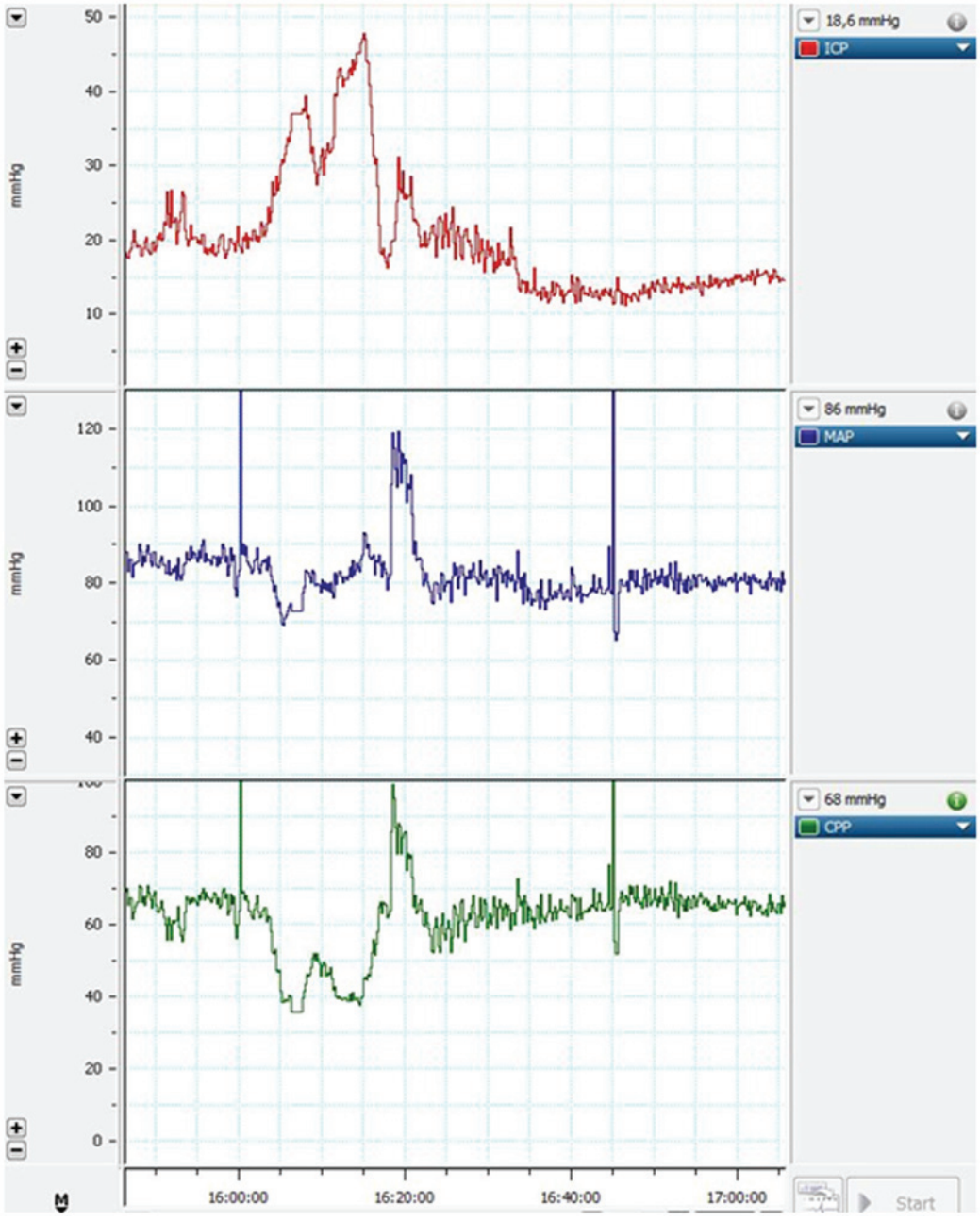

Figure 3. Intracranial pressure (ICP), mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) in a patient with traumatic brain injury undergoing bronchoscopy under general anesthesia with myorelaxants. ICP increased to 45 mmHg and CPP decreased concomitantly to 40 mmHg. Broncoscopy was stopped, further sedation given and manual hyperventilation administered briefly. ICP and CPP returned to normal levels.

dioxide tension ($PaCO_2$ and, in some series, correlation with actual CBF measurements was disappointing [29].

Microcirculation

Microcirculatory alterations play a key role in the pathogenesis of organ dysfunction. Brain endothelial cells help regulate vessel diameter and permeability [30], contributing to coupling of flow to metabolism [31]. Unfortunately, it is still not possible to visualize the brain microcirculation in clinical practice without direct exposure of the cerebral cortex after craniectomy and data on microvascular abnormalities in humans are limited.

Direct evaluation of the brain microcirculation can be performed using sidestream dark field imaging and

intravital microscopy [32]. These methods allow continuous and *in vivo* observation of the microcirculation at high resolution as well as evaluation of vessel size, number, density and flow. Although intravital microscopy is still considered the gold standard, it is not suitable for human use. The sidestream dark field technique can be applied on exposed cortical areas during craniectomy but care must be taken to limit pressure artifacts and minimize the risk of infection [33]. In patients with stroke from middle cerebral artery occlusion who underwent decompressive craniectomy, brain microcirculatory density and flow were significantly altered when compared to control patients [34]. Similarly, altered microvascular reactivity has been demonstrated in patients with SAH [35].

Brain tissue oxygen monitoring

Several techniques can be used to measure brain oxygenation, the most common in the ICU being jugular venous bulb oximetry and direct $PbtO_2$ measurement. Near infra-red spectroscopy has also been used for this purpose.

Jugular venous bulb oximetry

This technique requires placement of a catheter into the jugular bulb. The arterio-jugular difference in oxygen content ($AJDO_2$) is proportional to CBF and inversely proportional to oxygen consumption (cerebral metabolic rate for oxygen, $CMRO_2$) and is often used as a global measure of adequate perfusion. Proper positioning of the probe in the jugular bulb is crucial, since blood draining from extra-cerebral structures, such as the neck and face, can contaminate the lower portions of the jugular vein.

Under most conditions in which arterial hemoglobin saturation is constant, just the jugular oxygen saturation (SjO_2) is measured. This measurement can be performed by intermittent sampling, or continuously using fiber-optic probes. Normal values for SjO_2 in patients without brain damage are about 57% (95% confidence interval 52 to 62%) [36]. In the early hours after trauma, low SjO_2 values have been detected, especially in the most severe cases [37]. Severe and frequent SjO_2 desaturations are associated with worse outcome in TBI patients [38].

Because of the anatomy of the cerebral circulation, SjO_2 is an average indicator and a large volume of brain must be underperfused for an abnormality to be detected. Two-thirds of the blood flowing in each jugular vein comes from the ipsilateral and one-third from the contralateral hemisphere [39]; focal areas of mismatch between flow/metabolism can, therefore, be missed by this global measurement [40]. Additionally, SjO_2 values in one jugular vein may differ from values in the other [41]. Despite these limitations, intermittent SjO_2 sampling is a cheap and relatively easy tool for estimating adequacy of flow and metabolism, particularly when CBF is manipulated - for example, when using hyperventilation.

Direct $PbtO_2$ measurement

Direct $PbtO_2$ monitors are the most common technique used in the ICU to assess cerebral oxygenation. Probe positioning is crucial: usually inserted in the white matter, readings are dependent, in part, on proximity to intracranial pathology [42]. For example, if close to a contusion, values may be reduced and this should be considered when making management decisions. When the $PbtO_2$ probe is in what appears to be normal white matter on CT, then the reading, although local in nature, provides a reasonable estimate of global brain oxygenation.

$PbtO_2$ is not a 'surrogate' for ischemia or CBF, because it varies not only with CBF (and factors that regulate it - for example, CO_2 and MAP) but also with changes in arterial oxygen tension (PaO_2) among many other factors. $PbtO_2$ is, therefore, more a marker of the balance between regional oxygen supply and cellular oxygen consumption [9].

Monitoring $PbtO_2$ has been validated against fiberoptic SjO_2 monitoring, xenon-enhanced CT scanning, and SPECT. Threshold values vary slightly depending on what type of $PbtO_2$ monitor is used but values <20 mmHg are considered worth treating and values <15 mmHg indicate brain hypoxia or ischemia [43,44]. Decreases in $PbtO_2$ have been associated with independent chemical markers of brain ischemia in microdialysis studies [45]. The number, duration, and intensity of brain hypoxic episodes ($PbtO_2$ <15 mmHg) and any $PbtO_2$ values ≤5 mmHg are associated with poor outcome after TBI [46,47]. Episodes of brain hypoxia are common and may occur even when ICP and CPP are normal [48]. The exact relationship with outcome may, however, vary according to whether the probe is positioned in normal white matter, the penumbra or in a contusion [42,49]. Monitoring of $PbtO_2$ can be used in combination with other intra-parenchymal monitors, mainly ICP and cerebral microdialysis. Clinical studies suggest that therapy based on information from both an ICP and a $PbtO_2$ monitor may be associated with better outcomes than that based on ICP monitoring alone [50].

Near infra-red spectroscopy

Oxyhemoglobin, deoxyhemoglobin, and oxidized cytochrome oxidase absorb specific portions of the light spectra. When a tissue layer is illuminated with a source of light in the near infra-red wavelength, the attenuation of the light signal is correlated to the relative proportions of oxyhemoglobin and deoxyhemoglobin (HbO_2/Hb) and oxidized cytochrome oxidase in the tissue. Using appropriate calculations, an estimate of tissue oxygenation can, therefore, be made non-invasively and continuously.

Near infra-red spectroscopy has been used in TBI [51] and SAH [52], with ambiguous results. The technique has major limitations in adults: baseline normal values vary widely, extracranial contamination is a problem, and poor correlation with independent measurements of cerebral oxygenation has been reported frequently.

Microdialysis

Cerebral microdialysis (CMD) involves the insertion of a catheter tipped with a semi-permeable membrane (usually with a 20 kDa cutoff) in the brain parenchyma. The CMD catheter is constantly perfused, thereby allowing regular sampling of the patient's brain extracellular fluid [53]. CMD sampling is limited to the interstitial tissue area around the catheter, thus measuring regional brain metabolism. In clinical practice, a pattern of elevated lactate/pyruvate ratio and low glucose is considered as a warning sign for cerebral ischemia/hypoxia [54,55]. High lactate/pyruvate ratios in normoxic conditions have been interpreted as markers of hyperglycolysis. Elevated glutamate is a marker of cellular dysfunction, for example, delayed cerebral ischemia in high-risk SAH patients [56]. Absolute CMD values are important, but trends over time may provide more useful information. Recently, CMD has been used to identify the 'optimal' threshold for blood glucose during insulin therapy [57], and when used in combination with $PbtO_2$, CMD monitoring has potential clinical utility to target adequate values of MAP/CPP [58,59] and blood hemoglobin concentration [60].

Biomarkers

Neurological biomarkers, quantitative indicators of brain dysfunction or damage, may be obtained via sampling of biological tissues (blood, CSF, brain interstitial fluid), electrophysiological recordings, or neuroimaging. For soluble biomarkers, modeling of extracerebral concentration kinetics is complex and must account for passage across anatomical barriers into the bloodstream or CSF; serum levels of a marker may therefore correlate less closely with brain levels than with alterations in blood-brain barrier integrity. An emerging body of work suggests that multi-marker panels may enhance sensitivity and specificity for acute neurological injury [61,62]. There is also considerable interest in genomic, proteomic and lipidomic profiles.

Brain biomarkers are categorized according to their source as primarily neuronal, astroglial, or microglial. Here we briefly review the key biomarkers that have been tested clinically in acute neurological injury.

s-100β

Increased levels of this astroglial protein are associated with injury severity and are predictive of long-term death or severe disability in severe TBI [63,64], and following cardiac arrest [65] or aneurysmal SAH [66]. Although highly sensitive, the specificity of this marker for acute brain injury is generally low [67].

Glial fibrillary acidic protein

Glial fibrillary acidic protein is associated with intermediate filaments in astrocytes. Increased serum levels are observed following moderate and severe TBI [68], ischemic stroke [69], SAH [70], and cardiac arrest [71]. Serum glial fibrillary acidic protein levels more accurately discriminate TBI outcomes than do levels of s-100β [72].

Neuron-specific enolase

Neuron-specific enolase is an enzyme that is found in neurons, cells of neuroendocrine origin, erythrocytes and platelets. Increased serum neuron-specific enolase has been observed in patients with ischemic stroke, TBI, SAH and after cardiac arrest [63,65,73]. Neuron-specific enolase can help discriminate between favorable and unfavorable outcomes following severe TBI and cardiac arrest [63,65].

Tau

Tau is a neuronal protein that stabilizes microtubules, thereby promoting axonal transport. Significant elevations in tau have been observed in the CSF [74] and brain interstitial fluid [75] of patients with severe TBI. CSF tau protein is also elevated in patients with SAH, and is associated with neurological severity and outcome [76].

Amyloid β

Amyloid β is a peptide cleaved from neuronal and glial amyloid precursor protein. CSF amyloid β fragment levels are lower in TBI and in SAH patients than in control subjects, and lower levels are predictive of short-term functional outcome [77]. Recently, amyloid β has been measured in brain interstitium [75,78].

Neurofilament heavy chain

Elevated levels of NfH (neurofilament heavy chain), a neuronal protein that is integral to the axonal cytoskeleton, have been reported in the brain interstitial fluid of patients with severe TBI and are associated with physiological abnormalities and mortality [79]. CSF NfH is increased following SAH and hypertensive intracerebral hemorrhage [80,81]. Serum concentrations of NfH do not reliably identify brain injury, perhaps because the large size of this molecule impedes passage through the blood-brain barrier.

Ubiquitin carboxy-terminal hydrolase L1

CSF levels of UCH-L1 (Ubiquitin carboxy-terminal hydrolase L1) are significantly elevated in severe TBI

patients and are associated with lower levels of consciousness and worse six-month functional outcomes [82]. Serum levels of UCH-L1 are associated with TBI severity and survival [83].

Alpha II-spectrin

Alpha II-spectrin is a fundamental component of the neuronal cytoskeleton, which in the setting of injury is degraded into fragments referred to as spectrin breakdown products. CSF concentrations of these are elevated after TBI and correlate with the severity of injury and with six-month outcome [84]. Spectrin breakdown products are also detectable in serum and have diagnostic and prognostic value in children with TBI [85].

Electro-physiological measurements

Electroencephalogram

The classical indication for EEG is to detect and manage seizures, including status epilepticus. In critically ill patients, seizures are often non-convulsive and may aggravate brain injury [86]. Intermittent EEG is less sensitive than continuous EEG for detecting non-convulsive status epilepticus [87]. Approximately 50% of non-convulsive seizures are recorded within the first 60 minutes of EEG recording, but in some patients up to 48 hours of monitoring may be required [88]. Over the past decade, a more advanced form of EEG, quantitative EEG (qEEG), has been developed, in which the raw EEG signal is converted into a digital form using fast Fourier transformation (compressed spectral array) (Figure 4).

Several groups have used qEEG to detect seizures and other causes of brain dysfunction, such as ischemia. In SAH patients, the percent alpha trend variability (PAV) decreased acutely with the onset of vasospasm-induced decreases in CBF and returned to normal with treatment and resolution of vasospasm [89]. More recently, Rathakrishnan and colleagues [90] reported that changes in α power could help to distinguish delayed cerebral ischemia from vasospasm after SAH. Thus, there appears to be good evidence for the use of qEEG to detect cerebral ischemia.

qEEG may also be used to monitor the depth of sedation in the ICU. The most commonly used modality is the 'bispectral index' (BIS) [91], an algorithm-derived number that approximates the degree of sedation-induced EEG activity when patients are under general anesthesia. It ranges from 0 (brain dead) to 100 (normal brain function); a value of <60 indicates general anesthesia, and <30 indicates burst suppression.

Selected characteristics of raw EEG, such as the background rhythm and Synek scale, spontaneous variability and responsiveness stimulation, have been used to assist in estimating prognosis [92]. qEEG is more objective because it uses derived measures, and a larger amount of data that have been trended over time. The lack of PAV over time during the initial three days after severe TBI was associated with clinical outcome at 1 month [93] and 6 months [94]. PAV trends are automatically created by modern EEG software, and can be useful in tracking improvement or lack of improvement in patients in real time (Figure 5). Caution is required when using PAV and other qEEG parameters, however, because they may be affected by deep sedation.

Electrocorticography and spreading depression

Electrodes placed on the surface of the human cortex (electrocorticography), usually in proximity to damaged areas, can detect spontaneous waves of depolarization, which appear as spreading depression. Evidence is accumulating that these spreading depolarization waves cause an imbalance in energy consumption and delivery and may lead to secondary brain injury [95,96]. Spreading depression has been identified in TBI [97] and in patients with SAH [98] in whom the number of spreading depressions correlated significantly with the development of delayed cerebral ischemia even in the absence of vasospasm. Electrocorticography requires a craniotomy, but recent studies have suggested there may be correlates with human scalp direct and alternating current electroencephalography [99].

Evoked potentials

Somatosensory evoked potentials (SSEPs) are measured on the scalp as evoked EEG responses to an electrical stimulus applied typically to the median or tibial nerves. SSEPs are less affected by pharmacological agents or hypothermia than is the EEG. The main variable used for prognosis is the cortical response, which usually occurs at 20 msec after the stimulus, and hence is called the N20 peak. After cardiac arrest, bilateral absence of the N20 SSEP is associated with persistent vegetative state or death in all patients [100,101]. SSEPs can be measured during periods of sedation and even hypothermia, but most clinicians wait for return of normothermia. There is some concern about inter- and intra-observer variability in interpretation of SSEPs [102]. The use of so-called 'cognitive' potentials, such as N70, has been suggested to improve the predictive value of poor prognosis of this test but this approach is not widely used [103].

Imaging

Computed tomography

CT is the imaging modality of choice in the initial evaluation of patients with TBI or when acute hemorrhage is suspected. It helps to rule out surgical masses, and to identify early signs of intracranial hypertension. Since hemorrhagic lesions or edema may evolve over the first hours after injury, a CT scan must be repeated

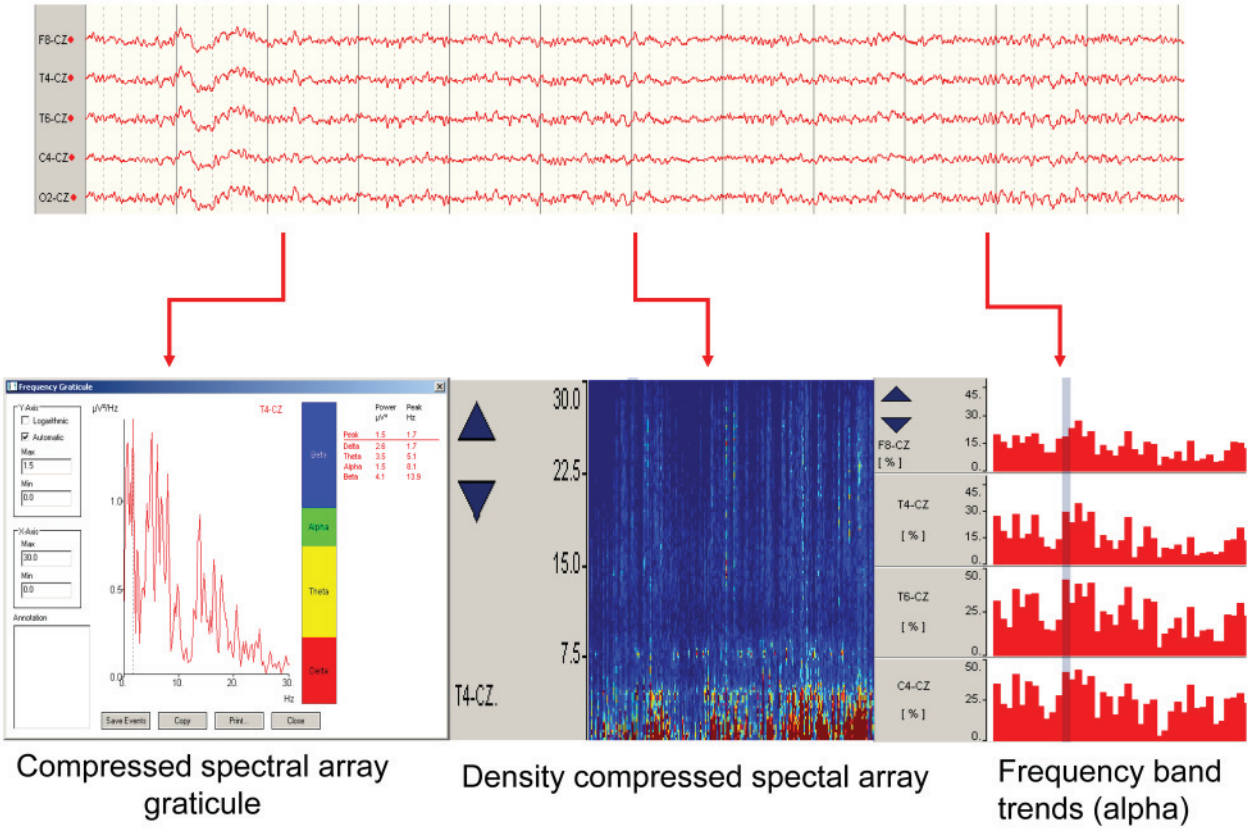

Figure 4. Transformation of raw electroencephalogram (EEG) into quantitative EEG (qEEG). The center top panel shows a 10 second segment of raw EEG. This EEG segment can be transformed using mathematical processing to separate the waves into major frequency bins with the height of each bin indicating the relative percentage (that is, power) of that frequency during the 10 second epoch (lower left panel). Each bandwidth can be trended on a minute by minute basis to create a variability histogram for that bandwidth for each channel (lower right panel). The alpha bandwidth variability trend is shown (lower center panel).

whenever there is clinical deterioration even if the initial imaging was apparently normal. The severity of TBI lesions may be classified using the Marshall [104] or Rotterdam [105] scales. New features, such as angioCT and CT perfusion, add important information to non-contrast CT and are increasingly used in stroke and SAH evaluation.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has great spatial resolution and, in patients with TBI, can identify pathologic abnormalities that are undetected or poorly characterized with CT, such as traumatic axonal injury. Acute ischemic stroke can also be detected earlier using MRI than CT. MRI is multi-parametric and can provide anatomical detail and quantitative information on brain physiology and metabolism, also allowing neuronal activation to be mapped. MRI has the advantage over other radiological methods in that it does not require ionizing radiation. Challenges for MRI scanning of critically ill patients include: monitoring and resuscitation devices that are incompatible with the magnetic field, the need for sedation or even neuromuscular blockade to prevent movement artifacts, and the risks inherent to transport outside of the ICU environment.

Specific MRI sequences can enhance the diagnostic and prognostic evaluation of patients with acute brain injury.

Diffusion weighted imaging

Reductions in the apparent diffusion coefficient (ADC), a marker of water diffusion, are associated with acute tissue infarction in stroke and in cardiac arrest. Reduced ADC values have been noted in major gray matter and white matter structures after cardiac arrest and are predictive of six-month outcome [106].

Diffusion tensor imaging

Diffusion tensor imaging evaluates the directional preference (anisotropy) of water diffusion and allows quantitative assessments of white matter damage in patients with TBI. The magnitude of fractional anisotropy

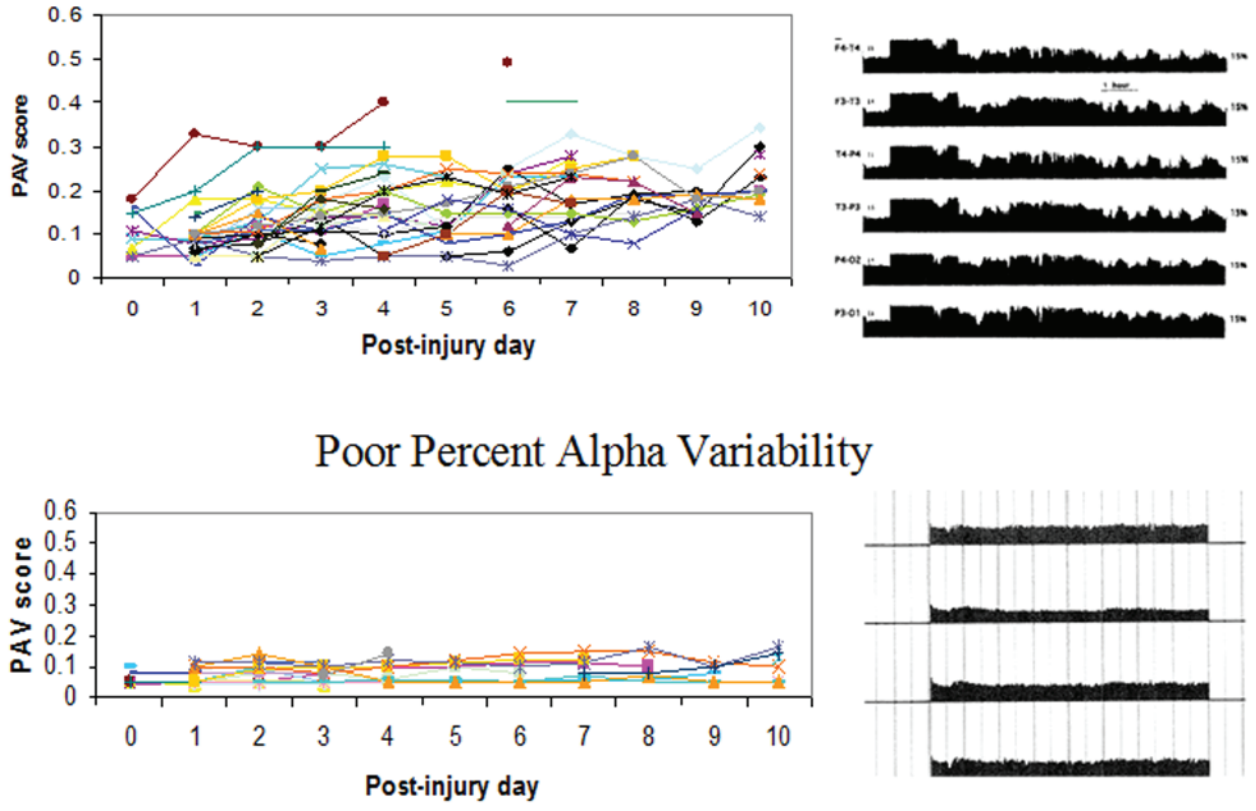

Figure 5. Lack of variability over time of the percent alpha trend (PAV) is associated with poor clinical outcomes. The daily PAV scores are graphed for those brain injured patients who eventually had a good outcome (top panel) and those that had a poor outcome (bottom panel). The PAV scores tend to remain good or improve day by day in those patients with a good outcome, whereas they remain poor or worsen day by day in those patients with a bad outcome.

change correlates with clinical TBI severity in the acute setting and with long-term outcomes [107,108].

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy measures tissue levels of selected neurometabolites and can provide important insight into TBI pathophysiology and natural history. It has been demonstrated that N-acetyl aspartate, a marker of neuronal integrity, is decreased in TBI, often in brain tissue that appears normal on cranial CT or on conventional MRI. Brain N-acetyl aspartate levels are associated with worse clinical condition and are predictive of functional outcome following TBI [108].

Susceptibility weighted imaging

Susceptibility weighted imaging is highly sensitive to microscopic hemorrhagic lesions associated with TBI, which are believed to represent a subtype of diffuse axonal injury. In children with diffuse axonal injury, the number and volume of hemorrhagic lesions seen with susceptibility weighted imaging correlates with neurological severity on initial presentation and with long-term cognitive impairment and functional disability [109].

Functional MRI

Functional MRI demonstrates that cortical-subcortical networks governing motor activity are significantly impaired following TBI [110].

Integration of variables

A single monitoring technique may not fully describe the complex pathophysiological changes in the brain and the concept of multimodality monitoring, the simultaneous digital recording of multiple parameters of brain function, has been introduced [111]. Multicenter collaborations, such as BrainIT (Brain monitoring with Information Technology collaborative network) [112], have demonstrated that recording of many physiological variables across multiple patients is feasible and can provide new clinical insights [113]. Advanced statistical and

mathematical tools can be applied to the large volumes of data obtained with the aim of identifying patterns of brain injury and providing clinicians with easier identification of specific targets [114]. Challenges in data integration and synchronization remain, but, ultimately, this concept should provide real-time, user-friendly advanced data analysis that, when applied at the bedside, could improve treatment.

Future trials

Neurological monitoring has developed rapidly over the past 25 years with widespread application of various monitors, but, although clinical studies suggest the physiological feasibility of this concept, there are still no published data from randomized trials to support that targeting any variables improves clinical outcome.

Neurocritical care research over the past 20 years has focused on the possibility that early pharmacological intervention might improve outcome, which has deflected attention from trials designed to answer simple questions about the everyday management of acute brain injury patients, such as optimum hemoglobin transfusion thresholds, hyperventilation, and arterial pressure management after hemorrhagic stroke, for example. More extensive availability and use of neuromonitoring technology should facilitate the development of large clinical trials networks to provide the infrastructure necessary to design and conduct studies to resolve some of these issues.

Conclusion

Monitoring of brain function in critically ill patients must begin with a careful clinical evaluation. Monitoring systems typically look at single variables and there is a need to integrate/combine systems in order to obtain a full and accurate assessment of the patient's condition so as to be able to select the most appropriate therapy. Importantly, neuromonitoring is a dynamic process and not a single measurement; the ability to follow changes over time is vital to assess response to therapy and predict prognosis. No monitor will, by itself, improve patient outcomes but wise interpretation of the data and integration of the information obtained into an individualized therapeutic plan should help optimize care of critically ill patients with brain injury.

Key messages

- Monitoring of brain function should be considered in all comatose patients in the ICU.
- Brain monitoring is centered on a careful clinical examination, although this can be limited in comatose and/or sedated patients.
- The goals of neuromonitoring are to: identify worsening neurological function and secondary insults that may benefit from specific treatments; improve pathophysiological understanding of cerebral disease in critical illness; provide physiological data to guide and individualize therapy; assist in prognostication.
- At present there is no 'ideal' single brain monitor; a combination of monitoring techniques may provide better insight into brain function than a single monitor used alone.
- Trends over time and threshold values are both important when assessing brain function.
- Clinical studies suggest the physiological feasibility and biological plausibility of management based on information from various monitors but data supporting this concept from randomized trials are still required.

Abbreviations

CBF, cerebral blood flow; CMD, cerebral microdialysis; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; GCS, Glasgow Coma Scale; ICP, intracranial pressure; MAP, mean arterial pressure; MRI, magnetic resonance imaging; PAV, percent α trend variability; $PbtO_2$, brain tissue PO_2; qEEG, quantitative EEG; SAH, subarachnoid hemorrhage; SjO_2, jugular oxygen saturation; SSEP, somatosensory evoked potential; TBI, traumatic brain injury; TCD, transcranial Doppler; TDP, thermal diffusion probe.

Competing interests

PLeR has received research funding from Integra and Neurologica and has received consultancy fees from Codman. PV is an advisor for Edge Pharmaceuticals, Intouch Health, and GE, has received grants from NIH, and has equity in Intouch Health. MO is supported by Grants from the Swiss National Science Foundation (grant nr. 320030_133103) and the European Critical Care Research Network (ECCRN). He is a member of the Speakers' bureau of Integra Neuroscience. GC has been involved in educational activities for Codman Italy and Codman Europe (Speakers' bureau). PJA has received honoraria from Integra life sciences and BARD/ Medivance. NS, RD, TS, FST and JLV have no conflicts of interest to declare related to this article.

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Published: 15 January 2013

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doi:10.1186/cc11513
Cite this article as: Stocchetti N, *et al*.: **Clinical review: Neuromonitoring - an update.** *Critical Care* 2013, **17:**201.