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Multimodality Neuromonitoring in Critically Ill Patients



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Without Primary Acute Brain Injury

This review focuses on the current experience with clinically available neuromonitoring techniques in critically ill patients at risk for neurological compromise, but without overt acute brain injury (ABI).

The field of neuromonitoring has grown rapidly over the past 30 years, which has helped improve pathophysiological understanding, clinical care and outcomes for patients with primary ABI, including traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), hypoxic-ischaemic injury and ischaemic or haemorrhagic stroke. The main goals of neuromonitoring are to better understand a patient's cerebral physiology, provide early detection of neurological worsening or cerebral dysfunction to avoid progression to irreversible neurological injury, and assist with neuroprognostication. This is accomplished through a combination of serial neurological examinations, neuroimaging studies, and continuously monitoring different neurophysiological parameters. Numerous expert opinion and evidence-based reviews on the role of multimodality neuromonitoring in ABI have been published, including a [consensus statement on multimodality monitoring in neurocritical care from the Neurocritical Care Society and the European Society of Intensive Care Medicine](#) (Stocchetti et al. 2013; Le Roux et al. 2014).

Most research and clinical practice in neuromonitoring has focused on patients with primary ABI, particularly TBI and SAH, and occurred in specialised neurocritical or neurotrauma care units (NCCUs). There is also a large population of critically ill patients without primary neurologic disease or ABI, who are at high risk for cerebral injury from their underlying disease process, systemic complications, or medical therapies, e.g. cardiac arrest, severe sepsis from extracranial sources, endocrinopathies such as diabetic ketoacidosis and hyper-/ hypo-thyroidism, renal and hepatic failure, rheumatologic conditions like haemophagocytic lymphohistiocytosis, and haematological abnormalities, including leukaemias and other neoplasms. The pathophysiology of secondary ABI in these patients is complex given the heterogeneous aetiologies and the numerous physiological cascades that can contribute to cerebral injury. Like ABI patients, these high-risk patients may benefit from neurophysiological and neurodiagnostic techniques to detect the antecedents of neurologic insults, thereby identifying a therapeutic window when neuroprotective or neurorestorative interventions will have the greatest likelihood of preventing and minimising irreversible brain injury.

Clinical Components of Multimodality Neuromonitoring

The traditional cornerstone of clinical neuromonitoring is the performance of serial bedside neurological examinations. The main components of the examination in a critical care environment comprise an assessment of the patient's mental status, including consciousness and awareness, cranial nerves and gross motor abilities. The [Glasgow Coma Scale \(GCS\)](#) is the most widely used scale for characterising a patient's degree of consciousness (Teasdale and Jennett 1974). Although it was originally developed to assess consciousness in TBI patients, its use has since expanded, becoming the most commonly used tool to communicate global neurological status for all ICU patients. It has been tested widely and has reasonable intra-rater and inter-rater reliability, although accuracy is greater amongst more experienced providers (Rowley and Fielding 1991). Concerns exist about its accuracy and usefulness in intubated patients and those receiving sedatives, analgesics and neuromuscular blocking agents (Kornbluth and Bhardwaj 2011). A newer scale to measure the degree of consciousness is the [Full Outline of UnResponsiveness \(FOUR\) score](#), which includes assessments of eye and motor responsiveness similar to the GCS, and adds tests for brainstem reflexes (pupil and corneal reflexes) and respiratory pattern (Wijdicks et al. 2005; Iyer et al. 2009). Both the GCS and FOUR score measures perform well at predicting in-hospital mortality and functional outcome (Wijdicks et al. 2011), although the utility of detecting subtle neurological changes in critically ill patients with these scales is unclear. Delirium is also a common manifestation of neurologic dysfunction in critically ill patients, and routine use of screening tools like the [Confusion Assessment Method for the ICU \(CAM-ICU\)](#) or the [Intensive Care Delirium Screening Checklist \(ICDSC\)](#) is recommended (Barr et al. 2013). Abnormalities detected while performing serial neurological examinations, whether on coma or delirium assessment scales, brainstem reflexes or detailed clinical examination could indicate the presence or evolution of ABI, and further investigation with neuroimaging or other diagnostic modalities may then be required.

Neuroimaging

Computerised tomography (CT) and magnetic resonance imaging (MRI) are the most frequently used modalities to diagnose or exclude intracranial pathology in critically ill patients. They are typically performed in response to new or changing neurologic signs or symptoms, and are not routinely used as screening tools. CT is commonly used to evaluate critically ill patients with an acute change in neurological status, and can

readily detect pathology like intracranial haemorrhage, hydrocephalus, and cerebral oedema, which may require emergency medical or surgical intervention. Portable CT imaging is now readily available and provides high quality images; because no patient transport is required this reduces the risk of transport-associated brain insults and complications (Peace et al. 2010; Swanson et al. 2010). MRI has greater anatomical resolution and a variety of specialised imaging sequences that provide detailed maps demonstrating subtle areas of infarction or haemorrhage, integrity of white matter tracts and quantitative information about cerebral physiology, perfusion, and metabolism. These images, however, are acquired at single time points during evolving systemic and cerebral disease processes. While these images can provide insights into disease pathophysiology, explain clinical symptoms and provide prognostic information, they always should be related to — and combined with — continuous neuromonitoring techniques and the clinical evaluation.

Electrophysiology

Continuous electroencephalography (cEEG) monitoring provides essential information while monitoring critically ill patients at risk for ABI. Continuous EEG is the only means to detect electrical (i.e. nonconvulsive) seizures and monitor response to anticonvulsant therapy. Seizures can be a manifestation of an occult cerebral insult, and in some circumstances they can aggravate existing brain injury. Current guidelines recommend cEEG monitoring in ICU patients without primary ABI who have “unexplained impairment of mental status or unexplained neurological deficits” to evaluate for nonconvulsive seizures (Claassen et al. 2013). Seizures occur in about 10% of ICU patients without primary ABI, with severe sepsis, renal failure and hepatic failure being the most significant risk factors (Oddo et al. 2009). Nonconvulsive seizures exclusively occurred in 67% of cases (Oddo et al. 2009). ICU patients with unexplained neurological dysfunction are typically monitored with cEEG for 24-48 hours (Gavvala et al. 2014). Seizures in critically ill patients are associated with poor outcomes and increased mortality. Additionally, EEG abnormalities (e.g. abnormal background frequencies, triphasic waves, etc.) have been associated with mortality in septic patients (Young et al. 1992). Although only currently used in patients with ABI from subarachnoid haemorrhage, characteristic trends on cEEG correlate with delayed cerebral ischaemia from vasospasm have been used at the bedside to supplement clinical data (Rathakrishnan et al. 2011; Vespa et al. 1997). Modules that quantitatively process EEG waveforms and graphically display information (e.g. compressed spectral array and colour density spectral array EEG) can also be used at the bedside for seizure detection and to monitor for patterns of cerebral dysfunction from causes like ischaemia.

Unlike EEG, evoked potentials are typically recorded as isolated snapshots and generally used to help estimate prognosis in select cases, e.g. bilateral absent N20 peaks after cardiac arrest rather than guide therapy (Wijdicks et al. 2006; Carter and Butt 2001). In addition, it is difficult to maintain the stability of EPs to perform continuous monitoring (Fossi et al. 2006).

Intracranial Pressure, Cerebral Blood Flow and Cerebral Autoregulation

Although intracranial pressure (ICP) and its consequences are discussed frequently in critical care patients, it is rarely measured directly (e.g. ventriculostomy or intraparenchymal monitor) in patients without ABI. Noninvasive techniques to estimate ICP include measuring optic nerve sheath diameter with ultrasound (Ohle et al. 2015; Rajajee et al. 2011), two-depth transcranial doppler (TCD) insonation of the ophthalmic artery (Ragauskas et al. 2012), TCD-derived pulsatility index (Bouzat et al. 2010), and computationally from the relationship between the arterial blood pressure and the middle cerebral artery (MCA) flow velocity waveforms (Schmidt et al. 2003). While these methodologies have shown encouraging results, they are mostly intermittent measures aimed at screening patients with clinical suspicion for increased ICP. The TCD-based approaches have the potential for continuous monitoring, but require constant adjustment of probe placement and have technical issues relating to device compatibility. In one study using a noninvasive TCD-based technique, ICP measurements in septic patients did not increase above 20 mmHg after fluid resuscitation. Calculated CPP levels below 60, however, were associated with increased neuronal injury, as assessed by S-100 β levels (Pfister et al. 2008a).

In circumstances when the clinical history, neurological examination and neuroimaging suggest cerebral oedema and that ICP increases may lead to ABI, invasive ICP monitors can be placed to accurately assess ICP and guide medical therapy. This has been done for patients with acute liver failure (Mohsenin 2013; Blei et al. 1993), diabetic ketoacidosis (Srinivasan et al. 2012) and drug intoxications (Marklund et al. 2007). In these patients, continuous ICP monitoring is more clinically useful than intermittent measurements.

Cerebrovascular pressure reactivity is the mechanism through which cerebral vessels protect the brain against inappropriate cerebral blood flow (CBF) changes, irrespective of acute changes in blood pressure or cerebral perfusion pressure (CPP). This is accomplished by the brain's intrinsic ability to dynamically adjust cerebrovascular tone or resistance. Dysregulation of this system can contribute to cerebral insults by several mechanisms, including ischaemia, hyperaemia, hypoxia, increased ICP and cerebral energy dysfunction. Cerebrovascular autoreactivity can be assessed in a dynamic fashion by interrogating the relationship between arterial blood pressure (ABP) or CPP and measures of cerebral blood flow or volume. Techniques to measure CBF used in this manner are MCA flow velocity via TCD, ICP, brain tissue oxygen (PbtO₂) and near-infrared spectroscopy (NIRS) (Zweifel et al. 2014).

Impaired cerebrovascular autoreactivity has been demonstrated after ABI and as a component of other systemic disease processes like severe sepsis (Taccone et al. 2010; Pfister et al. 2008b), liver failure (Macias-Rodriguez et al. 2015), and diabetic ketoacidosis (Ma et al. 2014). Some of the neurological complications in patients with these conditions may result in part from loss of cerebral autoregulation. There are currently no medical therapies to improve impaired cerebral autoregulation, although evidence exists that autoregulation may be optimised for an individual patient within a specified range of ABPs or CPPs and carbon dioxide levels (Taccone et al. 2010; Aries et al. 2012; Steiner et al. 2002). Additionally, sedative medications may influence cerebrovascular reactivity and this effect may be modulated by patient age and underlying disease process (Kadoi et al. 2008; Hinohara et al. 2005).

Cerebral Metabolism and Brain Oxygenation

Numerous pathological cascades that involve impaired brain oxygenation and cerebral metabolism exist. These can precipitate or exacerbate neurological insult in critically ill patients. Several monitoring modalities are available to interrogate brain oxygen, including direct measurement of brain tissue oxygen tension in a specific brain region (PbtO₂), global cerebral oxygen delivery via jugular bulb venous oxygen saturation (SjvO₂) and noninvasive cerebral oximetry in frontal brain regions with NIRS (Barazangi and Hemphill 2008; Maloney-Wilensky and Le Roux 2010; Stocchetti et al. 2013). There is limited experience with these techniques in patients without primary ABI, although the potential information learned about cerebral oximetry and metabolic function could prove helpful to predict, manage and prevent neurologic compromise in patients at high risk for brain injury.

A few studies have used these techniques to evaluate patients with sepsis with neurological symptoms (Oddo and Taccone 2015; Taccone et al. 2013). In septic patients with altered mental status, SjvO₂ and flow velocity in the MCA with TCD were measured during a dobutamine challenge. While CBF and oxygen delivery increased with dobutamine, oxygen consumption did not change (Berre et al. 1997). Another study found poor agreement between CBF estimates derived from TCD and NIRS (Toksvang et al. 2014). NIRS has potential wide applicability to examine for cerebral compromise, e.g. noninvasive evaluation of cerebral autoregulation in septic patients (Steiner et al. 2009), to assess cognition-related abnormalities in brain function in patients with mild hepatic encephalopathy (Nakanishi et al. 2014), to evaluate cerebral hyperaemia during treatment for diabetic ketoacidosis (Glaser et al. 2013), and to monitor cerebral function during volume resuscitation in dehydrated patients (Hanson et al. 2009). The best results however may be in neonates, and further study is required in adults.

Cerebral metabolism can be assessed through the sampling of the brain's extracellular fluid with surgically implanted cerebral microdialysis catheters. This technique provides an evaluation of regional cerebral bioenergetics; abnormal concentrations of certain cerebral metabolites (i.e. lactate, pyruvate, glucose, glutamate) can indicate evolving energy failure, hypoxia or ischaemia, or an imbalance between aerobic and anaerobic metabolism (Hutchinson et al. 2014; 2015). Most clinical experience with microdialysis is with ABI, and TBI and SAH in particular. However, it has been used in monitoring platforms of fulminant hepatic failure (Hutchinson et al. 2006; Tofteng et al. 2002). The ability of cerebral microdialysis to interrogate the brain's neurochemistry may increase our understanding of the pathophysiology of other systemic diseases that have neurological complications, like septic encephalopathy, diabetic ketoacidosis, toxic exposures, and assist in the critical care management of

these patients by providing targets to protect against cerebral energy failure. For example, in TBI patients, tight glycaemic control (80-120 mg/dL) with aggressive insulin therapy was associated with reduced cerebral glucose concentrations and worse cerebral energy crisis (Oddo et al. 2008; Vespa et al. 2012). Both high and low cerebral glucose have been associated with poor outcome in TBI. It is unclear what the optimal range for brain glucose is, what the relationship between serum and brain glucose concentrations in a metabolically stressed brain is, and how generalisable these findings are to other types of neurological insults (Hutchinson et al. 2015). However, knowledge about brain glucose may help guide therapy. In addition, understanding metabolism has shown that alternative fuels such as lactate may be beneficial in select patients (Oddo et al. 2012; Bouzat et al. 2014).

Conclusions and Future Directions

A major challenge to prevent brain injury in critically ill patients is that the progression from neuronal dysfunction to permanent injury typically proceeds undetected through a critical period when neuroprotective or neurorestorative interventions are likely to be effective. The goal of multimodality monitoring is to integrate signals in real time from a variety of technologies to provide bedside clinicians with a metric of the relative health or dysfunction of the brain before, during and after this critical period. Physicians can then use this information to guide individualised and goal-directed therapy to help prevent and mitigate further neurological injury. The integrative capabilities of bioinformatics platforms allow for the rapid synthesis and display of this data in a format that provides clinicians reliable information that can be used to target therapies (Hemphill et al. 2011).

Selecting the appropriate components of a multimodality platform must take into account the underlying pathophysiology of the relevant disease processes and potential mechanisms of cerebral injury. For example, neurological sequelae in patients with severe sepsis occur in multiple patterns including ischaemic strokes, vasogenic oedema and white matter abnormalities (Stubbs et al. 2013). Areas of perfusional ischaemia may result from impaired cerebral autoregulation or systemic hypotension, while other areas of injury may be the result of deleterious inflammatory mediated processes like endothelial cell swelling, microvascular dysfunction, alterations in blood-brain barrier permeability, and neurotransmitter imbalance. Thus, measuring cerebral autoregulation or microdialysis may detect actionable precursors to cerebral dysfunction in this population, whereas measuring ICP may be less helpful, because rarely is there enough cerebral oedema to increase ICP.

Choosing the most appropriate systemic and neurophysiological monitor is particularly important for patients who are at high risk for brain insult, but have not yet sustained brain injury. Currently, strategies to manage these patients are reactive in nature, with physicians responding to changes in neurological exam or physiological variables. Multimodality neuromonitoring has the capability to provide high-resolution real-time physiological data that, when computationally integrated and synthesised, can facilitate proactive measures to detect and correct neurophysiological derangements to avoid neurological compromise (Wartenberg et al. 2007). Furthermore, this paradigm will allow for an enriched understanding of the brain's response to systemic pathological states, and help design targeted treatment strategies that are mechanistically derived rather than empiric in nature. Overall, this rapidly evolving technology will provide physicians with additional information to promote brain health and avoid neuronal insult in critically ill patients.

See Also: [Sedation in Acute Brain Injury: Less is More?](#)

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