THIEME OPEN ACCESS

Multimodal Neuromonitoring: Current Scenario in Neurocritical Care

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Abstract

Keywords
► cerebral blood flow
► cerebral metabolism
► intracranial pressure
► cerebral perfusion pressure
► acute brain injury
► multimodal neuromonitoring
► neurocritical care

Multimodal neuromonitoring (NM) is the concept of integrating various tools and data to understand brain physiology and guide therapeutic interventions to prevent secondary brain injury. There exists a range of invasive/noninvasive and global/regional monitors of cerebral hemodynamics, oxygenation, metabolism, and electrophysiology that can be used to guide treatment decisions after neurological insult. No single monitoring modality is ideal for all patients. Simultaneous assessment of cerebral hemodynamics, oxygenation, and metabolism allows individualized patient care. The ability to analyze these advanced data for real-time clinical care, however, remains intuitive and primitive. Advanced informatics is promising and may provide us a supportive tool to interpret physiological events and guide pathophysiological-based therapeutic decisions. Available literature is not robust regarding multimodality NM and favorable patient outcome. This narrative review is undertaken to know the status and recent advancement of multimodal NM in neurocritical care.

Introduction

With the rapid technological advances in the recent years, neurocritical care has become one of the most emerging subspecialties catering to the needs of the critically ill patient with neurological dysfunction. Multidisciplinary specialists have now stood up on a common platform to provide efficient and expedient means of protecting the injured brain from further insult and ensuring improved recovery and overall outcomes. A significant portion of achievement should be credited to the simultaneous development of multimodal neuromonitoring (NM) techniques, which have evolved to obtain real-time information about the pathophysiology of injured brain (►Table 1). The goal of NM is to supplement the continuous evaluation of the neurologically injured patient beyond what serial neurological examinations and serial imaging can provide.

Although clinical assessment of comatose patients remains the gold standard, the detection of adverse events appears very late. Using various NM modalities, correction of physiological parameters can begin much before the irreversible damage. Given the pathophysiological complexity of brain injury, a single NM technique is unable to detect all instances of cerebral compromise. A multimodal NM strategy allows clinicians to better understand the pathophysiology and use individualized management within the context of protocolized care. In clinical practice, it is still not a standard of care. This narrative review is undertaken to know the status and recent advancement of multimodal NM in neurocritical care (►Table 2).

Definition

Multimodal NM encompasses integration of cerebral physiological parameters that assist intensive care unit (ICU) physicians in the management of brain-injured patients. These parameters include intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebral oxygenation, cerebral metabolism, and electrocortical activity.[1]

Indications

Multimodal NM has mostly been studied in patients with acute brain injury (ABI) (traumatic brain injury [TBI],

Table 1 Various multimodality neuromonitorings based on function

1	Clinical neurological evaluation	GCS, pupils, lateralizing signs, pupillometry
2	Cerebral flow-directed techniques	ICP, CPP, TCD, TDF
3	Cerebral autoregulation	PRx, Mx, ORx
4	Cerebral oxygenation-directed techniques	$SjvO_2$, $PbtO_2$, NIRS
5	Reflecting cerebral metabolism	Microdialysis, imaging
6	Reflecting cerebral global function	EEG, qEEG
7	Cerebral damage markers	S100B, NSE

Abbreviations: cEEG, continuous EEG; CPP, cerebral perfusion pressure; EEG, electroencephalography; GCS, Glasgow coma scale; ICP, intracranial pressure, NIRS, near-infrared spectroscopy; NSE, neuron-specific enolase; ORx, oxygen reactivity index; $PbtO_2$, brain tissue oxygen partial pressure; PR_x, pressure reactivity index, Mx, flow velocity index; qEEG, quantitative EEG; $SjvO_2$, jugular venous oxygen saturation; TCD, transcranial Doppler; TDF, thermal diffusion flowmetry.

Table 2 Various multimodality neuromonitorings and their recent advances

Multimodality neuromonitoring	Recent advances	Recommended targets
Clinical neurological evaluation	Infrared pupillometry	NA
ICP	1. ICP > 22 mm Hg as cutoff 2. Concept of overall burden (dose) of ICP 3. Optimal positioning in focal lesions 4. ICP data as color-coded plots for early warning and prognostication 5. Thrust on waveform analysis	Normal ICP in supine position: Adults: 5–15 mm Hg Children: 3–7 mm Hg Infants: 1.5–6 mm Hg Threshold for treatment: Adults: 22 mm Hg Children: 20 mm Hg
CPP	1. Proper positioning of arterial transducer at tragus 2. CPP_{opt} concept	Adults: 60–70 mm Hg Children: 40–50 mm Hg
CA	Low-frequency (minute to minute) signal processing instead of high-frequency (10 s): less data loss, better monitoring	Varies between –1 and +1 PRx >0.2: Impaired autoregulation PRx <0.2: Normal autoregulation
TCD	Transcranial color-coded duplex sonography	ECICA: 30 ± 9 (away) MCA:55 ± 12 cm/sec (toward) ACA:50 ± 11 cm/sec (away) $PCA_{segment\ 1}$:39 ± 11 cm/sec (toward) $PCA_{segment\ 2}$:40 ± 10 cm/sec (away) BA:41 ± 10 cm/sec (away) VA:38 ± 10 cm/sec (away)
TDF	–	Normal CBF in young adults: 50 mL/100 g of brain tissue/min (range 20–70 mL) The ischemic threshold: 18 mL/100 g/min < 10 mL/100 g/min irreversible damage
$SjvO_2$	1. Importance of estimation of arteriovenous oxygen content difference (a-vDO_2) (level III in BTF) 2. Multiple or sustained (> 10 min) desaturations—poor outcome	Normal $SjvO_2$: between 55%–75% Ischemic threshold: $SjvO_2$ < 50% for at least 10 min
$PbtO_2$	1. Most robust database among all oxygenation monitoring 2. Useful to guide the management of intracranial hypertension, to select the time and the type of treatment, and to monitor the effects of therapeutic interventions 3. Interventions to maintain $PbtO_2$ > 20 mm Hg 4. Stress on routine placement of probe in the normal-appearing brain, typically in the nondominant frontal lobe	The normal values: 35–50 mm Hg Threshold: Adults: ≤ 15–20 mm Hg Pediatric: ≤ 10 mm Hg

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Multimodality neuromonitoring	Recent advances	Recommended targets
NIRS	1. Noninvasive estimation of CA continuously 2. Ultrasound-tagged NIRS for continuous CBF 3. NIRS-based handheld device to screen intracranial hematomas in prehospital environment	The normal values: 60–80% Threshold not clearly defined
Microdialysis (CMD)	1. Concept of hyperglycolysis and neuroglycopenia after TBI 2. Use of CMD to differentiate ischemic from nonischemic etiology 3. Useful in neuroprotective drug trials 4. Availability of rapid sampling CMD	The normal value: Glucose: 1.7–2.1 mmol/L Lactate: 2.9–3.1 mmol/L Pyruvate: 151–166 µmol/L LPR 19–23 Glycerol: 50–100 µmol/L Glutamate: 14-16 µmol/L Threshold: Glucose ≤ 0.7–1.0 mmol/L LPR ≥ 40 Trend is more useful than absolute values
EEG	1. cEEG at least for 48 h for NCSE 2. qEEG 3. Invasive EEG more specific as compared to scalp EEG	NA

Abbreviations: ACA, anterior cerebral artery; BA, basilar artery; CA, cerebral autoregulation; cEEG, continuous EEG; CMD, cerebral microdialysis; CPP, cerebral perfusion pressure; CPPopt, optimal CPP; ECICA, extracranial internal carotid artery; EEG, electroencephalography; ICP, intracranial pressure; MCA, middle cerebral artery; NA, not applicable; NCSE, nonconvulsive status epilepticus; NIRS, near-infrared spectroscopy; qEEG, quantitative EEG; PCA, posterior cerebral artery; PbtO2, brain tissue oxygen partial pressure; SjvO2, jugular venous oxygen saturation; TCD, transcranial Doppler; TDF, thermal diffusion flowmetry; VA, vertebral artery.

subarachnoid hemorrhage [SAH], intracerebral hemorrhage [ICH], and acute ischemic stroke [AIS]) to detect early the secondary brain injury. It is indicated in sedated patients with Glasgow coma scale (GCS) < 9 and an abnormal brain computed tomography (CT) scan (intraparenchymal contusions/hemorrhages) in whom clinical examination is not reliable and who are at high risk for secondary cerebral damage, particularly elevated ICP, cerebral ischemia/hypoxia, energy dysfunction, and NCS. It is useful in guiding individualized, patient-specific therapy after ABI by optimizing the intracranial physiological milieu and also helps in prognostication (brain death patients). It can also be utilized as intraoperative monitoring during cardiac and carotid surgeries.

Various Neuromonitoring Modalities

Clinical Examination

Clinical assessment is the key component of NM; however, it is often confounded by sedation and muscle relaxation in comatose patients. Objective scales, such as GCS and full outline of unresponsiveness (FOUR) score, help standardize neurological state assessment. These help to identify changes by serial examination and also guide prognostication. Examination of pupil and documenting focal limb deficit (by medical research council scale) is also important.[2] Infrared pupillometry provides an objective assessment of pupillary reactivity and may be superior to its clinical assessment.[3] Subtle changes in intracranial physiology may not be detected by clinical examination, and alterations in the neurological state generally occur late. Clinical assessment should be supplemented by other NM techniques.

Intracranial Pressure

Direct measurement of ICP is the cornerstone of NM and standard of care following TBI in many neurosciences centers. Two methods of monitoring ICP are commonly used in clinical practice: intraventricular catheters and intraparenchymal microtransducer sensors (piezoelectric strain gauge [Codman microsensor and Raumedic Neurovent; Codman & Shurtleff, Inc., Massachusetts, United States] or fiberoptic [Integra Camino sensor; Integra LifeSciences, Tullamore, Ireland]). In addition to absolute ICP measurement, ICP monitoring allows calculation of CPP and assessment of intracranial compliance, cerebrovascular reactivity, and autoregulatory status.[4,5]

Several noninvasive methods for measuring and evaluating ICP have been developed. Optic nerve sheath diameter (ONSD), transcranial Doppler (TCD) ultrasonography, and pupillometry are noninvasive techniques that seem promising. By measuring the optic nerve with its sheath by ultrasound, specifically 3 mm behind the globe, ONSD can be measured. ONSD of 5 mm roughly correlates to ICP of 20.[6] TCD-derived pulsatility index (PI) > 1.6 has been associated with higher ICP values and worse outcomes.[7] The automated Neurological Pupil index (NPi), using pupillometer, reflects pupillary reactivity. NPi values range from 0 to 5, with values < 3 being associated with poor outcome and trend with elevated ICP.[8] The Vittamed 205 (Vittamed Corporation; Lexington, Massachusetts, United States) is a relatively newer noninvasive device that uses ophthalmic artery (OA) to measure ICP comparable to invasive ICP.[9] This self-calibrating device utilizes Doppler ultrasound to evaluate OA flow. However, evidence does not yet recommend the use of these

noninvasive techniques over invasive methods for real-time monitoring and treatment.[6,10]

The Brain Trauma Foundation (BTF) guidelines (2016) recommend ICP monitoring in all salvageable patients with severe TBI and an abnormal CT scan (presence of hematomas, contusions, swelling, herniation, or compressed basal cisterns) and also in those with a normal scan and two of the three high-risk characteristics (age more than 40 years, motor posturing, and systolic blood pressure less than 90 mm Hg). The current recommendations suggest treating ICP of greater than or equal to 22 mm Hg. It has shown to reduce in-hospital and 2-week post-injury mortality.[11]

Recent emphasis is on the concept of overall burden (or dose)—duration and severity of ICP—that decides prognosis, more so if it is refractory to treatment.[12] Currently, optimal positioning of ICP probe is emphasized, especially in focal lesions with mass effect as interhemispheric variations of over 10 mm Hg are reported.[13]

In the light of current evidence, it has been suggested that treatment strategies based merely on absolute ICP number may not always be beneficial. Rather waveforms should also be simultaneously analyzed.[14-16] ICP waveforms can indicate worsening pressure dynamics via the Lundberg waves.[17] It is now recognized that management strategies can be better guided by individual patient characteristics, interpretation of both ICP values and waveform and correlating with other NM variables. There is also recent interest in converting ICP data into color-coded plots for display using computer software for early warning and accurate prognostication.[18]

Autoregulation and Cerebral Perfusion Pressure

In a healthy brain, cerebral autoregulation (CA) acts to maintain constant CBF over a wide range of arterial blood pressure. Although deranged after ABI, CA still exists over a narrow range.[19] CPP is the principal determinant of CA. It is the net pressure gradient that drives oxygen delivery to cerebral tissue and is calculated as the difference between mean arterial pressure (MAP) and ICP. BTF (2016) guidelines recommend that CPP should be maintained between 60 and 70 mm Hg after TBI, with evidence of adverse outcomes if CPP is lower or higher.[11]

The Neuroanaesthesia Society of Great Britain and Ireland (NASGBI) and the Society of British Neurological Surgeons (SBNS) have issued a joint position statement regarding the calculation of CPP in the management of TBI. They recommend that the MAP used to calculate CPP should be the MAP estimated to exist at the level of the middle cranial fossa, which can be approximated by "positioning (zeroing) the arterial transducer at the level of the tragus of the ear." It is also recommended that the arterial transducer is repositioned, to remain in level with the tragus, after changes in head elevation.[20] Positioning (zeroing) arterial transducers at the level of the heart during CPP-based TBI management is discouraged.

The pressure reactivity index (PRx) is one of the most established methods to assess CA continuously. It is calculated as the moving Pearson's correlation coefficient between 30 consecutive, 10-s averaged values of ICP, and arterial blood pressure over a 4-minute period and varies between −1 and +1.[21] A positive PRx (> 0.2) signifies passive reactive vascular bed, whereas a PRx < 0.2 means normal autoregulation. PRx can be used for defining individual lower and upper limits of autoregulation, thus individualizing thresholds of CPP.[22] Plotting PRx against CPP results in a U-shaped curve in many patients, and the point where the PRx is most negative represents optimal CPP, that is, the CPP range in which autoregulatory capacity is most preserved in that injured brain.[23] Abnormal autoregulation defined by PRx monitoring is also a strong predictor of mortality and functional outcome after TBI.[24]

Standard high-frequency (second by second) signal processing to calculate PRx is technically demanding, time consuming, costly, and not widely available with standard monitors. To circumvent this problem, the recent study showed that low-frequency (minute by minute) assessment of ICP and MAP can provide same robust and relevant information for autoregulation monitoring.[25] In this study, a low-frequency autoregulation index, defined as the moving 1-minute correlation of ICP and arterial blood pressure calculated over time intervals varying from 3 to 120 minutes, was able to identify an optimal CPP recommendation that is no different than that obtained using standard high-frequency methodology. Therefore, there is less data loss, easy to use, and optimal CPP identification is possible for higher proportion of monitoring time.

However, since PRx and CPP$_{opt}$ are still reflecting the global autoregulatory capacity of the injured brain, the heterogeneous nature of injury goes unaccounted. Clinical relevance yet needs to be established.[26]

Cerebral Blood Flow

Alterations in CBF in association with impairment of autoregulatory reserve may cause or worsen secondary ischemic brain injury after TBI. CBF may be assessed directly or indirectly. Neuroimaging modalities particularly perfusion CT or MRI are frequently used in clinical practice for estimating CBF.[27] However, they provide a snap shot in time, whereas CBF is a dynamic process. Continuous direct monitoring of CBF would be helpful to manage acute neurologic patients.

Transcranial Doppler

Transcranial Doppler (TCD) is a noninvasive bedside monitoring technique that can evaluate real-time CBF hemodynamics in the intracranial arterial vasculature by examining Doppler shift caused by red blood cells moving through the field of view. It has the advantages of being inexpensive, reproducible, and portable in addition to high temporal resolution.[28] The flow velocity (FV) waveform resembles an arterial pressure pulse wave, and waveform analysis permits quantification of peak systolic, end diastolic, and mean FVs. The PI, which provides an assessment of distal cerebrovascular resistance (CVR), can also be measured.[29]

Based on FV signals and PI, several secondary, advanced model-based analyses of cerebral hemodynamics have been introduced, such as CA, noninvasive ICP and CPP estimation, and critical closing pressure.[30]

TCD has found its application in neurocritical care in a variety of conditions including TBI, aneurysmal SAH, stroke, and brain death. TCD has been most widely used in aneurysmal SAH for detecting vasospasm and guiding therapeutic interventions.[31] Developing or established cerebral vasospasm is diagnosed when middle cerebral artery (MCA) FV exceeds 120 to 140 cm/s or if there is more than 50 cm/s/day increase from the baseline value. For angiographic vasospasm, mean MCA FV above the threshold value of 100 cm/s and for clinical vasospasm values above 160 cm/s give the most accurate picture.[32] The sensitivity and negative predictive value of TCD for prediction of delayed cerebral ischemia (DCI) is very high (90% and 92%, respectively).[33] However, in almost 40% of patients with clinical DCI, it can show normal FV never exceeding 120 cm/s; so, it should be used cautiously rather causes other than vasospasm and inter individual variability shall be considered.[34] Newer TCD color-coded duplex sonography helps improve its predictive value by visualizing difficult to insonate vessels such as ICA and ACA.[35]

Thermal Diffusion Flowmetry

should be used cautiously rather causes (TDF) is an invasive, quantitative method for continuous monitoring of CBF in neurocritical-care patients as it provides absolute measurements with a high temporal resolution, potentially allowing for bedside intervention that could mitigate secondary injury.[36] The commercially available system includes the Hemedex monitoring system, which is not magnetic resonance imaging (MRI) compatible.[1]

The TDF catheter consists of a thermistor heated to a few degrees above tissue temperature and a second, more proximal, temperature probe. The temperature difference between the two is a reflection of heat transfer that is converted into an absolute measurement of blood flow in mL/100 g/min. The probe is inserted in the white matter, 20 to 25 mm below the dura where the normal range of CBF is around 18 to 25 mL/100g/min.[37] Continuous monitoring of CBF with TDF and CPP allows calculation of flow-related autoregulation index.[38]

Like TCD, TDF also is a handy bedside monitor to detect vasospasm in aneurysmal SAH. Ideally, probe should be placed in white matter of the vascular territory deemed at risk for vasospasm.[37] TDF has been validated by Xenon perfusion CT, and CBF level below 15 mL/100g/min is identified as a reliable cutoff for diagnosing symptomatic vasospasm.[37] Quantification of rCBF with TDF is highly dependent on patient's core body temperature and is significantly altered in conditions of hyperthermia.[39] Moreover, TDF provides useful data for only 30 to 40% of monitoring time because of monitor dysfunction secondary to placement errors and missing data during recalibrations.[39]

Cerebral Oxygenation

Following neurological insult, a direct relationship between cerebral hypoxia and poor outcome has been addressed in many studies.[40,41] Management of severe TBI based on combined ICP and brain tissue oxygenation monitoring has shown to reduce brain tissue hypoxia with a trend toward lower mortality and more favorable outcomes than only ICP-guided treatment.[42,43] There are several invasive and non-invasive continuous methods of monitoring regional or global brain oxygenation.

Jugular Venous Oxygen Saturation

Measurement of Jugular Venous Oxygen Saturation ($SjvO_2$) can determine adequacy of the balance between global CBF and cerebral metabolic demands ($CMRO_2$).[44] $SjvO_2$ monitoring involves retrograde insertion of a fiberoptic catheter into the internal jugular vein (dominant side) and advanced cephalad beyond the inlet of the common facial vein into the jugular bulb at the base of the skull. Correct placement is confirmed when the catheter tip is level with the mastoid air cells on the lateral neck radiograph (level with the bodies of C1/C2).[45]

Ratio of $CMRO_2$ and CBF is constant as the two are coupled under normal physiological conditions. The difference between the oxyhemoglobin saturation of cerebral arterial and mixed venous (i.e., internal jugular) blood represents the oxygen extraction. Thus, a low $SjvO_2$ (i.e., a high oxygen extraction ratio) may indicate low CBF in relation to $CMRO_2$. The normal range of $SjvO_2$ is 55 to 75%.[46] In addition to measuring venous oxygen saturation, this technique allows estimation of arteriovenous oxygen content difference ($a-vDO_2$) and lactate by intermittent sampling. Value of $a-vDO_2$ above 9 mL/dL probably indicates global cerebral ischemia and values less than 4 mL/dL indicate hyperemia.[1]

Multiple or sustained (> 10 minutes) desaturations ($SjvO_2$ < 50%) are associated with poor outcome in TBI patients.[47] BTF (2016) guidelines recommend maintaining $SjvO_2$ > 50% and monitoring for arteriovenous oxygen content difference to help guide management decisions (level III).[11] $SjvO_2$ is a global, flow-weighted measure that may miss critical regional ischemia. After early enthusiasm, its clinical use has decreased in favor of other methods of monitoring brain tissue oxygenation.[48]

Brain Tissue Oxygen Partial Pressure

Brain tissue oxygenation pressure ($PbtO_2$) represents the interaction between plasma oxygen tension and CBF and is useful in providing focal measurement of cerebral oxygenation.[49] In this, a micro-sensor is inserted via a skull bolt or through craniotomy into the penumbra area or frontal subcortical white matter. Two commercially available micro-sensors allow direct, continuous measurement of brain tissue gases. Licox measures brain $PbtO_2$ using a polarographic Clarke-type electrode, whereas Neurovent-PTO uses fiberoptic technology to measure $PbtO_2$, $PbCO_2$, and PH. Both

these sensors are approximately 0.5 mm in diameter and use thermocouple to measure brain temperature as well. A "run-in" or equilibration time of up to 30 minutes is required before readings are stable.[45]

PbtO$_2$ is normally lower than arterial PaO$_2$ due to the extravascular placement of probes and high metabolic activity of the brain.[50] Normal PbtO$_2$ values range from 25 to 50 mm Hg. In the clinical setting, values of PbtO$_2$ 15 to 25 mm Hg, < 15 mm Hg, < 10 mm Hg, and < 5 mm Hg are indicative of moderate brain ischemia, critical brain ischemia, severe brain ischemia, and cell death, respectively, although PbtO$_2$ is best interpreted in the context of duration as well as depth of ischemia.[51] Recent guidelines recommend interventions to maintain PbtO$_2$ > 20 mm Hg after TBI.[52]

PbtO$_2$ has most robust evidence among all cerebral oxygenation-monitoring techniques, and multiple studies have demonstrated an association between low PbtO$_2$ and poor outcomes after TBI independent of ICP and CPP.[41,42,53,54] There is recent suggestion to routinely place probe in normal appearing brain, typically in the nondominant frontal lobe.[55] As with ICP therapy, a stepwise management approach is also used for PbtO$_2$ augmentation, which includes optimization of MAP/CPP, respiratory manipulations, and blood transfusions (in the setting of anemia). It helps select the time and type of treatment and monitoring the effects of therapeutic interventions. Some of the reported problems of this monitoring include its focal nature, trauma due to catheter insertion with subsequent gliosis, and the limited ability to adequately position and secure sensors in precise position.

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a noninvasive technique used for observing real-time changes in regional cerebral oxygenation at the bedside.[56] The physical principle of NIRS is based on the ability of light waves of near-infrared wavelength (i.e., 700–1,000 nm) to penetrate the scalp, skull, and brain to a depth of a few centimeters. These light waves are differentially absorbed by oxygenated hemoglobin (HbO$_2$), deoxygenated hemoglobin (Hb), and cytochrome aa3 (CytOx). Quantification of this optical attenuation is achieved using reflectance spectroscopy based on the modified Beer-Lambert law. Measurements are obtained by placing optodes on one side of the forehead with an interoptode spacing of 4 to 7, thereby estimating oxygen content of all vascular compartments (arterial, capillary, and venous).[45] The measurements reflect relative concentrations of HbO$_2$, Hb, and CytOx. The normal values of rSO$_2$ are reported to be 60 to 80%. A 20% decline in rSO$_2$ from baseline is considered an ischemic threshold.[57]

NIRS has been used to monitor patients with TBI, ICH, and in patients undergoing carotid endarterectomy. In one study in patients in the ICU following head injury, NIRS detected 97% of desaturations, whereas jugular venous oximetry detected only 53%, and NIRS was more specific and more sensitive.[58] NIRS has also been used to determine cerebrovascular pressure reactivity and optimal CPP noninvasively.[59] NIRS can be easily combined with TCD, and simultaneous use of both these modalities provides useful information about

hemodynamic and metabolic cerebral adaptive status in patients with neurological insult. Recently, ultrasound-tagged NIRS for measurement of CBF has been used to monitor CA continuously during cardiac surgery.[60] NIRS technology is used in development of handheld device to screen intracranial hematomas in prehospital environment.[61] Although the future holds promise for the development of a single NIRS device with capability to noninvasively measure cerebral hemodynamics, oxygenation, and metabolism over multiple regions of interest,[62] routine NIRS monitoring is currently not recommended in adult TBI patients.[63]

Cerebral Metabolism

Brain metabolism can be assessed by hourly microdialysis measurement of cell substrates (glucose), metabolites (lactate, pyruvate, and glycerol), and neurotransmitters (glutamate) in the extracellular fluid.[64] Cerebral microdialysis (CMD) consists of inserting a specialized catheter tipped with a semipermeable dialysis membrane, usually with a 20 kDa cutoff, in the brain parenchyma. The CMD catheter is constantly perfused with a cerebrospinal fluid-like solution, thereby allowing regular (usually every 60 minutes) sampling of patient's brain extracellular fluid into micro-vials and bedside analysis using manufacturer's device.[65] The catheter should be placed perilesionally in focal brain injuries, in the right frontal region for diffuse TBI, and in ACA-MCA watershed region or region of vasospasm on the side of aneurysm rupture for SAH.[66] Glucose < 0.8 mM and lactate-to-pyruvate ratio (LPR) > 40 warrant intervention.[67] Elevated LPR precedes clinical DCI by 11 to 13 hours in SAH patients.[68] CMD detects early hypoxia and ischemia and increases the therapeutic window to avoid secondary lesion.

CMD has been applied to patients in many different clinical situations, including TBI, SAH, epilepsy, ischemic stroke, tumors, and during neurosurgery.[69] Recently, it has been instrumental in identifying hyperglycolysis and increased glucose utilization post-TBI.[70] Combined monitoring of CMD and systemic glucose is, therefore, helpful in individualizing glucose targets.[71] CMD can distinguish ischemic from nonischemic hypoxia. Increased LPR in the presence of low pyruvate suggests ischemia, whereas in the presence of normal pyruvate, it suggests nonischemic etiology such as mitochondrial dysfunction.[67] Recent interests are in exploring the usefulness of CMD during neuroprotective drug trials.[72] Recently, a continuous rapid sampling CMD has also been described for research use; however, it is not yet available for clinical purpose.[29] CMD has contributed substantially to our understanding of the pathophysiology of brain injury, but its clinical utility is still debated and there are very little data to confirm whether CMD-guided therapy can influence outcomes. Although primarily a research tool at this point, CMD is complimentary with other NM modalities.

Electroencephalography

Seizures occur in 20 to 40% of TBI patients, and early detection and treatment are crucial to minimize the burden

of seizure-related secondary injury.[44] More importantly, neurocritical care comatose patients often (4–30%) have nonconvulsive seizures (NCS) that are difficult to diagnose clinically.[73] Intermittent EEG monitoring has a sensitivity of only 50% to diagnose NCS compared to over 90% when continuous electroencephalography (cEEG) is performed for 48 hours. Invasive EEG monitoring using subdural strip or intracortical depth electrodes allows detection of seizures that are not visible on standard (scalp) EEG monitoring.[74] Cortical spreading depolarization (CSD) and quantitative EEG (qEEG)–derived indices such as the alpha power or the alpha/delta ratio can be used to detect DCI in poor-grade SAH and severe stroke patients.[68,75]

Integration of continuous EEG into NM strategies identifies associations between seizures, intracranial hypertension, and cerebral metabolic derangements, and offers prognostic information.[76,77] Current multimodal NM guidelines recommend EEG in all patients with ABI and unexplained altered consciousness and in patients with convulsive status epilepticus who do not return to baseline within 60 minutes after medication, during therapeutic hypothermia, and within 24 hours after rewarming.[75]

Somatosensory Evoked Potential

Continuous somatosensory evoked potential (SSEP) monitoring is able to detect neurological deterioration after ABI and is used for the purpose of prognostication.[78] A bilateral absent cortical SSEP response is a strong predictor for poor neurological outcome in patients with a postanoxic coma.[78] Prolongation of the central conduction time (CCT) in comatose patients has been associated with worse long-term prognosis. The CCT is the difference between the latencies of the responses recorded over the cervical spine and that recorded over the sensory cortex. In SAH, prolongation of the CCT is associated with transient neurological deficit, and it precedes the development of these deficits.[78] The changes in CCT are related to cerebral ischemia.[79]

Biomarkers

Biomarkers, as NM tool, are used for diagnosis and prognosis of neurological diseases and can be qualitative and quantitative cerebral damage markers.[80] They may be present in blood, CSF, or saliva. They can predict pathophysiology, response to treatment, and side effects. In TBI, markers such as $S100\beta$, UCHL-1, and glial fibrillary acid protein (GFAP) are used as surrogate markers of imaging to reduce cost and exposure to radiation.[80] Use of $S100\beta$-like markers has already been integrated into some clinical guidelines to stratify patients for CT imaging during the acute phase, although not widely accepted.[81] Markers such as $S100\beta$ and neuron-specific enolase (NSE) directly relate to the extent of brain damage after the event.[80] Risk of posttraumatic epilepsy (PTE) can be predicted by markers such as IL1-B gene in conjunction with EEG.[80] Postinjury

cognitive decline can be predicted by markers such as Tau protein.[80]

Integrating Multimodality Neuromonitoring

Recent clinical investigations by several independent groups show feasibility and utility of brain multimodality NM. The aim of this is not to add new variables for an intensivist to chase but to integrate information from multiple modalities to formulate a patient-specific "injury profile" that will guide formulation of an optimal treatment plan. Because of the number and complexity of monitored physiological variables and the interplay between them, computational analysis and integration of data are essential prerequisites for the presentation of user-friendly and clinically relevant information at the bedside.[82] Commercial systems are available to process and display multiple data streams although these can be individualized based on the needs of individual institutions or researchers.

Future Directions

Future goals should be directed to integrate multiple NM monitoring and development of computer-assisted methods so that even diverse range of data from all these modalities can be interpreted with greater accuracy, thus facilitating appropriate decision making for patient management. We may consider incorporating patient demographics and imaging to the multimodality NM to make it more individualized. Emphasis should also be stressed on development of user friendly, bedside devices for rapid diagnosis of cerebral physiological alterations ahead of major neurological insults. We are still looking out for impact of multimodal NM on the clinical outcome. Collaboration of large international databases, prospectively collected from standardized observational studies for comparative effectiveness, is the need of the hour. Examination of not just neuromonitors but titrating these with management strategies based on data so acquired will have to be done. This will open doors to better therapeutic options.

Conclusion

There is ample evidence to suggest superiority of multimodal NM over individual NM parameters. The focus is toward individualized targeted treatment based on real-time physio-logical parameters obtained by various continuous NM devices. There is an automatic cross-validation set between different variables that increases the confidence of treat-ment decision making. Recent technological advances in multimodal NM are taking place gradually, which aim to make these more user friendly, are able to acquire faster and precise data in accordance with patient clinical condition, are able to predict outcome, and are available to wide group of neurointensivists. High-quality outcome studies are still crucial for its widespread implementation and acceptability.

Conflict of Interest
None declared.

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