MULTIMODALITY BRAIN MONITORING

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Introduction

Multimodality monitoring (MMM) is perhaps the hottest topic in Neurocritical Care in 2017. There have been several important consensus articles and statements published since September 2014 (Chestnut; LeRoux; Stochetti; Hutchinson). I refer the reader to those important articles for in depth discussion of the topics.

Overview of MMM

Neurocritical care for central nervous system injury from trauma, stroke or brain hemorrhage requires specific and timely diagnosis, monitoring and treatment based upon specific information gathered from the brain. Early after a brain injury the brain experiences increased vulnerability to secondary insults. These insults can take the form of cytotoxic brain edema, repeat ischemia, fever-related injury and seizures, just to name the most common ones. Secondary insults are frequently silent and are expressed only once the problem becomes critical. The timely diagnosis of these secondary insults is important to overall survival of the brain. Multimodality monitoring refers to the tracking of several parameters of brain physiology and function that can be affected by direct medical or surgical intervention. These parameters include intracranial pressure monitoring, brain electrical activity (continuous electroencephalography - cEEG), brain oxygenation (jugular venous and brain tissue oxygen pressure-PbrO2), cerebral blood flow, depth EEG, neurochemistry (cerebral microdialysis), and intracranial pressure. Monitoring of the brain requires the sometimes conflicting requirements of being sensitive yet specific, regional yet global, and immediately accessible yet remotely available. In the past 18 months, several publications have called our attention to this emerging field and provide guidance in the application of these important new tools to critical ill neurologic patients. Figure 1 outlines these invasive techniques.

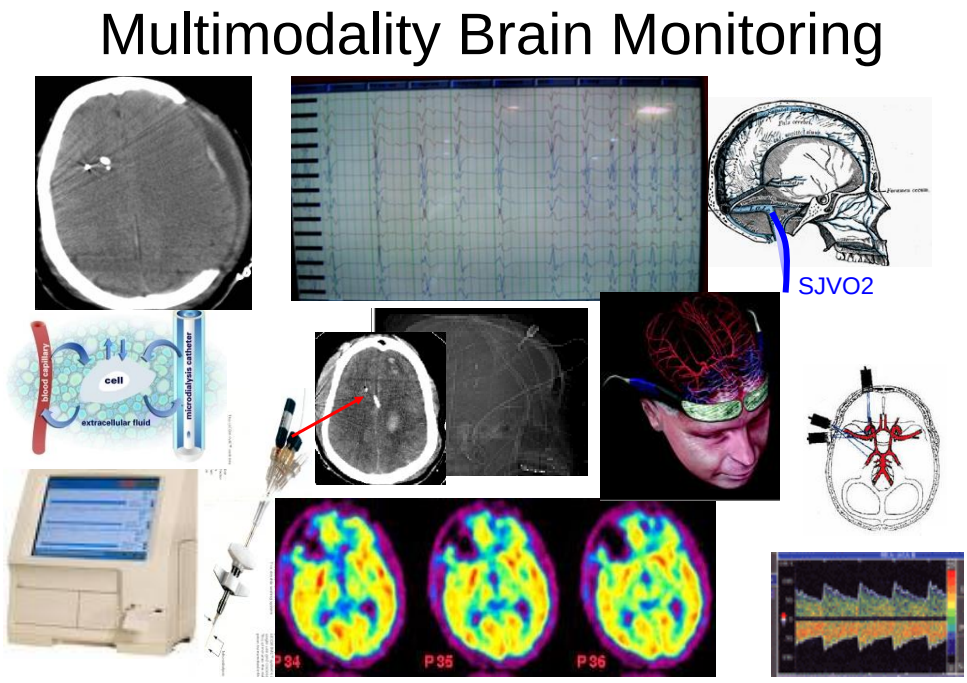

Figure 1: Multimodality Monitoring: A series of brain monitors that often used in conjunction in the patient with coma.

Intracranial Pressure Monitoring (ICP)

ICP monitoring is a bedrock of MMM (LeRoux et al, 2014) and needs to be performed for most patients who have intracranial MMM. The exception would be those patients who have ICU EEG Monitoring alone. ICP monitoring has been recently challenged by the BEST TRIP study (Chestnut 2012). However, careful analysis of the BEST-TRIP study has been done and a consensus interpretation has now been published (Chestnut 2015). In this latter consensus publication seven important conclusions were reached. The top 3 are outlined here: 1) "The BEST-TRIP study compared two ICP treatment protocols and is not a study of ICP monitoring of the efficacy of ICP monitoring". 2) "The primary impact of the BEST TRIP study should be research oriented", and 3) "For those currently monitoring ICP, the results of the BEST TRIP trial should not change practice". Combined with important discussions the 2013 NCS MMM Consensus conference and resulting articles on ICP (Chestnut 2014; Helbok 2014) and MMM overall (LeRoux 2014).

ICU Continuous EEG

Over the past five years, it has become increasingly apparent that seizure activity commonly occurs in critically neurologic patients. Vespa et al (1999) initially demonstrated that over 20% of patients with traumatic brain injury demonstrated seizures while in the ICU, half of which were non-convulsive seizures that were detected only by the use of continuous EEG. These seizures can be regional in the area of the primary insult, such as adjacent to a temporal lobe contusion, or can be more widespread involving the entire brain. Operational parameters for optimal brain cEEG have been established but some variability still remains. In a similar study, Vespa et al (2003) demonstrated that over 26% of patients with non-traumatic intracerebral hemorrhage demonstrated seizures on cEEG, and that these seizures were independently associated with progressive brain edema and midline shift. Thus the seizures may be eliciting progressive secondary injury and promoting clinical deterioration. Laboratory studies (Roncati Zanier et al 2003) as well as clinical data (Vespa et al 2004) now confirm that post-traumatic seizures are not benign and may lead to additional neurologic injury and cell death, especially in vulnerable regions of the brain such as the hippocampus. Figure 1 demonstrates an electrographic seizure. Identification of seizures and early treatment may preclude this secondary deterioration. In a similar report from another major neurocritical care center, Claassen (2004) used similar cEEG methods and detected an 18% incidence rate of seizures in a mixed population of intracerebral hemorrhage, subarachnoid hemorrhage and ischemic stroke. The seizure rate in brain hemorrhage patients was higher than that in ischemic stroke (Vespa et al 2003) which may be due to the toxicity of intraparenchymal blood and pro-epileptic effects of iron deposition in the brain. Pandian et al (2004) reported that combined video-EEG monitoring was useful in detecting seizures in the ICU and found similar incidence rates of seizures. The addition of video information about clinical behavior confirms the previous findings that many seizures can be sub-clinical and therefore not detectable by clinical manifestations alone. Several studies indicate high incidence of seizures in comatose patients with SAH, TBI, ICH, and cardiac arrest Claassen (2004, Vespa et al 2003, Claassen and Vespa, 2014). This is true to both adults and children (Abend 2013) and seizures can negatively affect outcome (Topjian 2013). Thus, seizures occur after primary brain injury, appear to be related to progressive neurologic damage and can be easily detected by available cEEG methods.

cEEG monitoring is now considered mandatory for the treatment of refractory status epilepticus (Brophy 2012). cEEG can be used to detect nonconvulsive seizures, guide therapeutic decisions for antiseizure medications, and be useful in predicting outcomes for refractory status epilepticus. Guidelines for the rapid start of cEEG monitoring in the treatment of status have now been established (Brophy 2013; Josephson 2017-in press).

The hurdles to performing cEEG include: 1) Available expertise in reading EEG, 2) automated seizure detection, and 3) remote access to EEG for real-time reporting. Several new digital EEG instruments are currently available that provide for remote access as well as automated seizure detection. In our hands, we have launched an internet-available remote expert review system that permits remote access and assessment of the EEG. This telemedicine approach has resulted in decreased interval between event detection and intervention. Direct feedback to nurses in the form of confirmation of seizure detection and record review as well as the ability to teleconference increases accuracy of seizure detection. In addition, the telemedicine approach creates the potential for expanding the limited list of experts to centers that presently lack sufficient human experts.

Depth EEG is now available for invasive EEG monitoring. Waziri and colleagues (2009) have published recently on the use of this technique. There appears to be a high incidence of seizures that are seen with the depth EEG that are not seen on surface scalp EEG in comatose patients. Vespa and colleagues (2016) have demonstrate a high incidence of seizures after TBI and that these seizures and periodic discharges were associated with

worsening metabolic crisis. Witsch and Claassen (2017) have demonstrated the periodic discharges are associated with reduction in cerebral oxygenation, which adds merit to the claim that seizrues and period discharges are injurious in the acute brain injury period.

Table 1 demonstrates selected studies regarding cEEG monitoring.

Study on ICU cEEG	n	Seizure incidence (%)	Diagnostic groups	Impact on care
Jordan 1995	124	35	Coma from variety of diagnoses	1, 2
Vespa 1999	91	22	TBI	1, 2
Vespa 1999	300	21	TBI, SAH, ICH	1, 2
Vespa 2003	65	28	ICH	1, 2
Claassen 2004	204	17	SAH	1, 2
Pandian 2004	105	42	Coma from variety of diagnoses	1, 2, 3
Young 2005	55	20	Coma from variety of diagnoses	1, 2
Ronne-Engstrom 2006	70	33	TBI	1, 2
Claassen 2007	102	28	ICH	1, 2
Oddo 2008	201	22	Sepsis and Medical ICU diagnoses	1, 2, 3
Vespa 2010	140	23	TBI	1, 2, 3
Rittenberger 2012	101	12	Cardiac Arrest	1, 2, 3
Mani 2012	38	23	Cardiac Arrest	1, 2, 3
Wusthoff 2013	26	65%	Cardiac Arrest	1, 2, 3
Topjian 2013	200	43%	Pediatric coma for many reasons	1, 2, 3, 4
Abend 2014, 2015	130	20%	Coma for many reasons	1, 2, 3, 4
O'Neil 2015	144	30%	Pediatric TBI	1, 2, 3
Williams 2016	41	93%	Pediatric Coma suspected seizures	1, 2, 3
DeMarchis 2016	402	12%	SAH	1, 2, 3, 4
Vespa 2016	34	61%	TBI in Coma	1, 2, 3
Witsch 2017	90	23%	SAH	1, 2, 3, 4

Table 1: A listing of cEEG monitoring studies that outlines the impact of this monitoring tool on patient care. Impact on patient care codes are 1) assists in diagnosis, 2) Guides or changes therapy, 3) Changes treatment, 4) Improves neurologic prognosis.

In summary, cEEG monitoring during the acute injury period is an important feature of modern neurocritical care. Early seizures and periodic discharges should be considered at least potentially injurious to the patient. Treatment strategies based on cEEG are being created and will need to be tested in the future.

Intracranial Brain Monitoring

The use of intracranial brain monitoring has become increasingly popular for comatose patients with brain injury, subarachnoid hemorrhage, brain hemorrhage or other causes of coma. Usually, these monitors are inserted similarly to and in conjunction with intracranial pressure monitors. A recent consensus statement regarding MMM has been endorsed by the Neurocritical Care Society (Leroux 2014). Figure 2 demonstrates the appearance of several small probes in a region of brain. We will explore these probes including brain tissue oxygen probe (PbtO2), cerebral blood flow probe, cerebral microdialysis, and depth EEG.

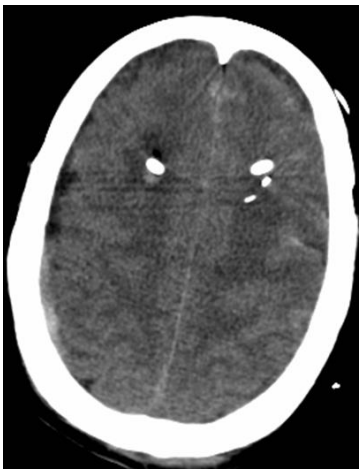

Figure 2: multiple intracranial brain monitors appearing as hyperdensities in the brain.

Cerebral Oxygenation

Preserving cerebral oxygenation in the setting of brain injury, edema and potentially secondary injury is of paramount importance in the critically ill brain. Several lines of evidence from clinical brain injury research suggest that ischemia occurs frequently in traumatic brain injury. The initial 12 hours after injury appear to be most critical in which brain oxygenation monitoring studies have demonstrated a 30% incidence of brain ischemia in the brain injury population. Moreover, autopsy series have demonstrated that necrotic cellular changes are frequent in fatal TBI and these changes are thought to be due to ischemia, rather than other mechanisms of cell death. Recent PET studies done in TBI patients both early and late after the injury demonstrate that brain ischemia can occur, especially with provocative maneuvers such as hyperventilation. Diringer and colleagues performed PET studies at a mean of 12 hours post injury and demonstrated areas of potential ischemia. Similarly, Coles and colleagues used oxidative PET studies in TBI patients and found that at baseline CO2 of 30-34 mm Hg, the mean ischemic brain volume was 67 cc. This volume of ischemic brain tissue increases with provocative hyperventilation and potentially can lead to permanent tissue injury. Excessive hyperventilation can promote brain ischemia. Thus, the brain has a potential for ischemia and monitoring the brain during intensive care unit treatment adjustments, such as modifying the mechanical ventilator, requires an assessment of brian oxygenation. Until recently, cerebral perfusion pressure (CPP) has been used to estimate the degree of cerebral blood flow and to avoid ischemia. However, several studies have questioned the validity of CPP (Vespa, 2003; Vespa 2004). Thus, direct monitoring of tissue oxygenation and oxygen utilization appear to be better than monitoring CPP alone to determine the adequacy of cerebral oxygenation.

There are presently two clinically available modes of brain oxygenation monitoring, jugular venous saturation (SjO2) monitoring (a global method) and brain tissue oxygen (PbrO2) pressure monitoring (a regional method). SjO2 monitoring has been well established to have prognostic significance and clinical utility in detecting ischemic as well excessively hyperemic states of cerebral blood flow and oxygen supply. Indeed, hyperemia was the most common disturbance of cerebral blood flow as associated with alteration of brain metabolism (Glenn et al, 2003), in which cerebral blood flow is increased disproportionately to the need for oxygen utilization. Hyperemia is thought to occur because of impaired cerebral autoregulation and has been associated with poor outcome, especially in pediatric brain injury populations (Vavilala 2004). The ability to monitor cerebral blood flow in real time and to adjust blood pressure and ventilation parameters to avoid either extreme of hyperemia or brain ischemia has become a powerful tool in the treatment of global brain edema resulting from brain injury.

In contrast to global cerebral oxygenation monitoring, PbtO2 monitoring provides regional assessment of oxygenation, in the format of a brain sensor that resembles an intracranial pressure monitor. The PbrO2 value is thought to represent the partial pressure of oxygen in the brain and is considered a marker of the balance between oxygen supply and utilization. The PbrO2 is not a measure of oxidative metabolism per se, but in general can reflect changes in oxygen utilization as a function of the oxygen supply. In the last year, several interesting papers on PbrO2 have been published and have resulted in several new concepts. 1) PbrO2 can decrease even in the setting of adequate cerebral perfusion pressure. Menzel[26] (2003) notes concurrent transient drop in PbrO2 when CPP decreases below 70 mm Hg. Since it is generally agreed that PbrO2 reflects that balance of supply

and demand of oxygen in the brain, these data suggest that a CPP below 70 mm Hg results in a critical limitation of oxygen supply compared to ongoing demand. In similar studies of combined PbrO2 and CPP monitoring, a lower CPP threshold of > 60 mm Hg was found to be the critical threshold. 2) PbrO2 increases with supplemental oxygen and in turn this increase in PbrO2 is associated with improvement in brain metabolism.

In general, PbtO2 is placed into normal appearing brain. Normal values are 20-40 mm Hg. With brain ischemia, the values decline to < 15 mm Hg. Treatments to augment PbtO2 include provision of supplemental inspired oxygen (FiO2), elevation of blood pressure, blood transfusion, and moderate hypercapnia.

There have been several important recent studies on brain oxygen monitoring. The most influential one is the BOOST 2 study (Diaz-Arrastia). This was a phase 2 randomized controlled safety study to assess the value of monitoring brain tissue oxygen and intervening for low PbtO2 values. The study was a huge success in demonstrating safety of PtbO2 monitoring and demonstrating improved clinical outcomes in those patients who were assigned to the monitoring arm. The results of this study suggest that several diverse interventions for low PbtO2 are feasible and safe. A phase 3 study is now being planned.

Cerebral Blood Flow

Hemedex® cerebral blood flow monitor is a novel device to monitor regional CBF in comatose patients. Few published studies are available for this technique, but it appears to be promising.

Brain Neurochemistry and Metabolism

Brain metabolism can be monitored using an invasive probe in brain tissue, with real time results. This technique is called cerebral microdialysis. Cerebral microdialysis is performed using a CMA70 probe (10cm flexible shaft, 10 mm membrane length, 20 kD cutoff, CMA, Stockholm, Sweden) inserted via a twist drill burr hole adjacent to an existing ventriculostomy. The microdialysis catheters are inserted into a depth of 1.5 - 2 cm below the skin at an angle 30 degrees lateral to the scalp. The probes are tunneled 3 cm under the skin and secured to the scalp with a flat profile, and then attached to the CMA103 perfusion pump. Normal saline is perfused through the catheters at 0.3 uL/min and fluid was collected in 60 minute samples and then placed into dry ice or directly into the CMA600 instrument. The initial 60-minute sample is not used for analysis as time is allowed for stabilization of the probe. Microdialysis is not interrupted for transport or bedside testing. Important changes in brain metabolism including brain ischemia and non-oxidative metabolic crisis can be determined using cerebral microdialysis.

Several groups working independently have performed chronic microdialysis monitoring in humans after TBI and have demonstrated low concentrations of extracellular glucose (Hutchinson, 2015; Vespa et al 2003). Extracellular glucose decreases to undetectable levels with complete loss of brain function due to brain death whereas less severe reductions in extracellular glucose can occur due to ischemia, seizures (Vespa 2003), spreading depolarizations (Fabricius 2006), and for reasons that are unclear. Extracellular glucose can be at very low concentrations for long periods of time, up to 30% of the ICU course, and occur without any change in intracranial pressure or cerebral perfusion pressure (Vespa 2003). Low extracellular glucose concentrations have been associated in some cases with increased lactate, suggesting that an increase in anaerobic metabolism resulted in glucose consumption. However, in other studies, low glucose occurred in the absence of elevated lactate (Vespa 2003). In several reports, the low extracellular glucose concentrations were associated with increased mortality (Hutchinson 2015) and poor neurologic outcome at 6 months (Vespa 2003). Thus, the available evidence suggests that low extracellular glucose frequently occurs and thus there may be limited supply of glucose to the brain after TBI.

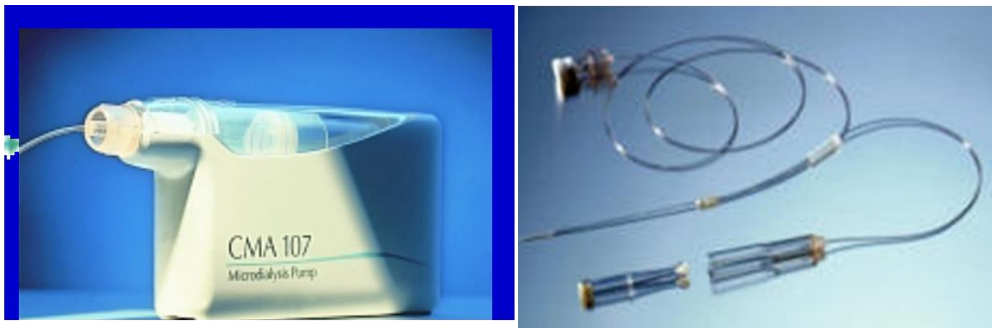

Figure 3: cerebral Microdialysis monitoring devices with automated pump (left) and catheter with collection vial (right).

Summary of MMM

MMM can be useful in the treatment of comatose patients. The following table outlines the monitoring modality and levels of evidence for particular clinical conditions.

Modality	Clinical Diagnosis	Indicator	Impact on Care	Levels of Evidence
ICP	TBI, SAH, IVH, Coma	ICP > 20	Mortality	Mostly II, Level I
EEG	Status Epilepticus	Seizures	Mortality	II
EEG	Cardiac Arrest	Seizures	Prognosis	II
EEG	TBI	Seizures, qEEG	Prognosis	II
EEG	SAH	qEEG	Stroke,DCI	III
Depth EEG	TBI, SAH	Seizures, Spreading depression	Prognosis, DCI	III
PtbO2	TBI	PbtO2 < 20	Mortality, Functional outcome	I
PbtO2	TBI	PbtO2 < 20	Prognosis	II
PbtO2	SAH	PbtO2 < 20	Vasospasm	II
Microdialysis	TBI, SAH	LPR	Prognosis	II
Microdialysis	TBI	Glucose	Glucose control	I

MMM is a powerful set of tools for the comatose brain injured patient. The treating neurologist plays a central role in performing and/or interpreting this information. The expected range of care options in the future will include these techniques. Evidence based medicine studies already exist but randomized trials remain yet to be done.

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