Microdialysis in the Neurocritical Care Unit

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KEYWORDS

• Microdialysis • Neuromonitoring • Traumatic brain injury • Subarachnoid hemorrhage

KEY POINTS

- Microdialysis is a neuromonitoring technique for direct measurement of cerebral metabolism.
- Microdialysis has a role in traumatic brain injury and subarachnoid hemorrhage, and the clinical applications continue to expand.
- Microdialysis may be used as a research tool for studying the cerebral effects of medications, pathophysiologic mechanisms, or other cerebral metabolic processes.

INTRODUCTION/HISTORY

Monitoring the brain after acute injury is central to the practice of neurocritical care and is analogous to hemodynamic monitoring for the cardiovascular system. However, the most widely available clinical monitor, the physical examination, is unavailable in neurologically compromised or sedated patients. Current neuromonitoring techniques have evolved from the study of cerebral physiology and allow for the repeated or continuous measurement of multiple cerebral parameters. These measurements may detect evolving abnormalities and thus guide interventions designed to minimize secondary injury after neurosurgical interventions, traumatic brain injury (TBI), or subarachnoid hemorrhage (SAH).[1] However, no monitor alone can improve patient outcome. Only actions such as decompressive craniectomy for increased intracranial pressure (ICP), based on monitoring data, carry the prospect of improving outcome, and for microdialysis (MD), this aspect requires further studies.

Many neuromonitoring devices attempt to assess changes in cerebral metabolism. This process may be indirectly estimated from global imaging modalities such as xenon computed tomography (CT) and through measuring cerebral oxygen content with jugular venous oxygen saturation ($SjvO_2$) catheters and cerebral oxygenation (partial pressure of oxygen in brain tissue [$PbtO_2$]) probes. Direct metabolic substrate measurement in the living human brain currently can only be achieved with cerebral MD catheters or positron emission tomography (PET) scans, which can only be done at great cost and for 1 or 2 time points.

The use of small (approximately 1 mm) semipermiable coaxial and loop membrane tubes within the brain was first described by Bito and colleagues in 1960 and was later refined in 1972 with the advent of the coaxial MD catheter by Delgado

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and colleagues. In 1986, the first data on neurotransmitter concentrations in the rat brain were reported by Tossman and colleagues.[2]

The first human implantation occurred in 1987 in adipose tissue and was followed in 1990 with the first use in human cerebral tissues.[3] In 1992, the first clinical use of this device was reported, and the creation of commercially available catheters and bedside analysis systems followed shortly.[2,4–6] Over time, MD has gained popularity in trauma, stroke, and aneurysmal SAH, and, as more studies verify its usefulness, the indications for use will continue to expand. As of 2012, about 12 centers in North America and about 30 worldwide clinically use brain MD on a regular basis.

MD MEASUREMENT

The Device

The monitoring device consists of a double-lumen dialysis probe that is implanted within the cerebral tissue (**Fig. 1**). A physiologic fluid (artificial cerebrospinal fluid [CSF] or normal saline without lactate or glucose) is passed into the probe and over the dialysis membrane using a micropump injector. The concentration gradients between the probe fluid and the surrounding tissue cause various molecules to diffuse across the membrane and into the solution, which is collected and analyzed in sampling vials or passed over a detector system such as a glucose oxidase–based electrochemical sensor.[7] This fluid analysis is not a direct measure of the extracellular concentrations because the concentration in the dialysate depends on the membrane (pore size and surface area), the rate of the fluid flow, the size of the extracellular space, and the individual solutes' rates of diffusion. It is therefore termed the relative recovery.[6]

There are commercially available 20-kD and 100-kD cutoff membrane probes; however, at the present time, only the 20-kD (CMA70, CMA Microdialysis AB, Solna, Sweden) probe has been approved by the US Food and Drug Administration for human use in the United States and Japan. In Europe, clinical trials with the 100-kD MD probe for the measurement of cerebral intercellular cytokines, neurotrophic factors, and biomarkers are ongoing.[8–11] A flow rate of 0.3 μL/min is used for 10 mm of membrane length using a 20-kD cutoff membrane. With these settings, the flow recovery rate of CMA70 is approximately 70% for small molecules such as glucose, lactate, pyruvate, glutamate, and glycerol.[12,13]

Once the device is assembled and secured, the system allows hourly sample collection with bedside, computerized analysis. The device consists of the MD probe, connection tubing, perfusion media, pump, and collection device (see **Fig. 1**).[2] Commercially available assays currently

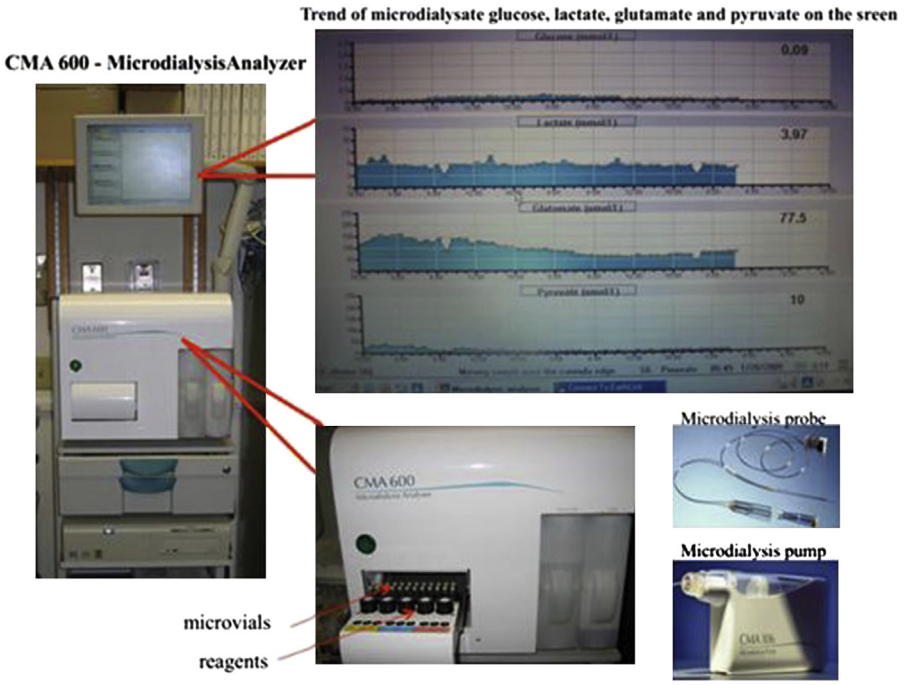

Fig. 1. Components of MD. The device consists of the MD probe, connection tubing, perfusion media, pump, and collection device. The MD analyzer then presents the data in a variety of formats including the trends over time.

include glucose, lactate, pyruvate, glycerol, and glutamate, in a 12-μL sample aliquot (**Table 1**). At present, the cost of the setup is approximately $120,000 ($60 per probe and $110,000 for the CMA 600 analyzer and pump). Thus, frequent use lowers the cost substantially per patient.

Reimbursement, and Cost Recovery

Several Swedish neurointensive care centers, such as Karolinska, Lund, and Uppsalla have shown that use of MD data can contribute to improved clinical decision making in the most severely injured patients with TBI and SAH. Nursing, critical care, and neurosurgical staff use data from MD to aid decisions, such as vasospasm management, ventilator weaning, choice of oxygen saturation, CSF drainage, and decompressive craniectomy. However, data to justify the cost of MD in terms of improved patient outcome are lacking. In European Union countries, costs have historically been amortized over general patient care and intensive care unit costs, but, in the countries of itemized billing, such as the United States, most centers have funded early MD experience from research grants.

Chen and colleagues[13] recently showed that MD costs can be successfully covered by using inpatient billing codes 99291, and 99292. The procedural code 61105 was introduced to cover twist-drill craniostomy and placement of monitoring catheters with devices such as MD.

Device Implantation

The probe tip is implanted through a twist-drill craniostomy or at the time of surgery. The dura is incised, and the catheter tip is passed to the appropriate depth. This insertion may be done freehand and then tunneled through a skin incision away from the skull defect, or the MD catheter may be a part of a bundled, bolt-based system. The freehand method allows for more precise anatomically selected positioning of the catheter tip but is more labor intensive because the bundle allows for the simultaneous placement of other monitoring devices such as ICP monitors and $Pbto_2$ probes.

Because the present system may only sample a small tissue zone, estimated to be about a 10-mm sphere around the catheter tip, several locations are potential targets for device implantation. For TBI, probes placed directly into contusions have been shown to yield severe derangements in metabolism consistent with tissue death and are unresponsive to any manipulations, and therefore this location is not recommended.

Egstrom and colleagues[14] investigated the placement of MD catheters within the penumbra zones as well as within the anatomically normal brain. They found a statistically significant difference in the glucose, lactate, lactate/pyruvate ratio (LPR), glutamate, and glycerol levels between the two catheter locations. Thus, placing the probe in structurally normal tissue may aid in assessing the global cerebral metabolic condition, and placing the probe in pericontusional tissue may provide direct data on the microenvironment of the potentially salvageable tissue.[5] For aneurismal SAH, insertion of the device in the parent artery distribution aids in the detection of vasospasm and may be achieved at surgery for aneurysm clipping.[15]

STANDARD BIOMARKERS OF CLINICAL RELEVANCE (WITH 20-KD MD)

The range of investigational molecule analytes continues to expand, but glucose, lactate, pyruvate,

Table 1
Normal value of small molecule analytes that may be measured with commercially available reagents and analyzers such as the CMA 600 (collected with conventional 20-kD cutoff membrane)

Parameters	Clinical Significance	Normal Value (Mean ± SD)
Glucose	Decrease in hypoxia/ischemia	1.7 ± 0.9 mmol/L
Lactate	Increase in hypoxia/ischemia	2.9 ± 0.9 mmol/L
Pyruvate	Decrease in hypoxia/ischemia	166 ± 47 μmol/L
LPR	Best marker for anaerobic metabolism Increase in hypoxia/ischemia	23 ± 4
Glycerol	Increase with the destruction of cell membrane structure and free radical generation	82 ± 44 μmol/L
Glutamate	Increase in hypoxia/ischemia and excitotoxicity	16 ± 16 μmol/L

Abbreviations: LPR, lactate/pyruvate ratio; SD, standard deviation.

Data from Reinstrup P, Stahl N, Mellergard P, et al. Intracerebral microdialysis in clinical practice: baseline values for chemical markers during wakefulness, anesthesia, and neurosurgery. Neurosurgery 2000;47:701–10.

glycerol, and glutamate levels are the current standard for cerebral metabolism available from a 12-μL sample with the CMA analyzer device.[4] These data in combination with other monitoring tools such as ICP monitors, $Pbto_2$ probes, $Sjvo_2$ catheters, electroencephalography, and other modalities are commonly used in the intensive care unit.

Glucose, the primary energy substrate, is initially transported from the extracellular fluid into the cell cytoplasm and, through glycolysis, it is converted to pyruvate. Pyruvate is then aerobically metabolized in the mitochondria through the citric acid (TCA) cycle (**Fig. 2**). Under normal circumstances, 95% of the cerebral energy requirements come from the aerobic conversion of glucose to water (H_2O) and carbon dioxide (CO_2). Through this process, ATP synthesis is highly efficient and results in the generation of 38 molecules of ATP for each molecule of glucose:

$$1\ \text{glucose} + 6O_2 + 38\text{ADP} + 38\text{Pi} \rightarrow 6CO_2 + 6H_2O + 38\text{ATP}$$

Under hypoxic conditions such as TBI, conversion of glucose can only take place by anaerobic glycolysis because of mitochondrial dysfunction, and only 2 molecules of ATP and 2 molecules of lactate are generated for each molecule of glucose:

$$1\ \text{glucose} + 2\text{ADP} + 2\text{Pi} \rightarrow 2\ \text{lactate} + 2\text{ATP}$$

With normal aerobic states, pyruvate and the reduced form of nicotinamide adenine dinucleotide (NADH) are taken up by mitochondria, and their oxidation by the TCA cycle and respiratory chain provide most of the ATP production. With the anaerobic state, reoxidation of NADH through the respiratory chain is blocked and must instead occur by the reductive conversion of pyruvate to lactate by lactate dehydrogenase (LDH) (see **Fig. 2**). Thus, an increase of the LPR indicates failure of oxidative phosphorylation and may portend future or ongoing cerebral injury from ischemia or hypoxia.[5,15–19]

In general, the LPR normal range averages 23 ± 4 (mean ± standard deviation [SD]),[20] and the mean normal glucose values are 1.7 ± 0.9 mmol/L (see **Table 1**).[6] However, metabolic crisis may occur at a glucose less than 0.8 mmol/L with an LPR greater than 25, and thus several investigators have suggested the MD may indicate brain tissue at risk of delayed damage caused by high ICP or vasospasm.[20–22]

An additional target molecule, glycerol, is an integral component of cell membranes. The loss of

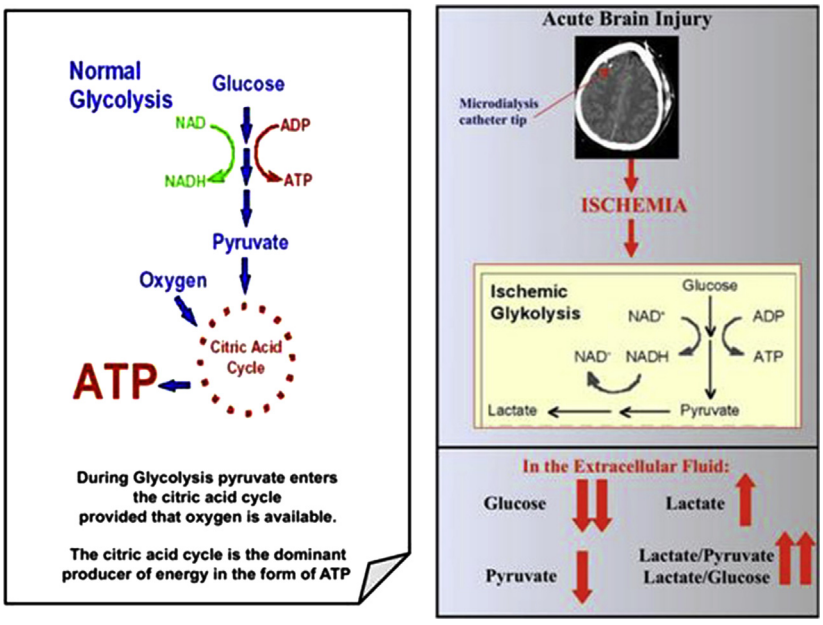

Fig. 2. Aerobic and anaerobic glycolytic cascade. Glucose is taken into the cytoplasm of neuronal cells and used as the main energy substrate. Under normal circumstance, 38 molecules of ATP are generated in the TCA cycle. Under hypoxic conditions, conversion of glucose takes place by anaerobic glycolysis, and 2 molecules of ATP and 2 molecules of lactate are generated. Under these conditions, reoxidation of the reduced form of nicotinamide adenine dinucleotide (NADH) through the respiratory chain is blocked and must instead occur by the reductive conversion of pyruvate to lactate by lactate dehydrogenase (LDH). NAD, nicotinamide adenine dinucleotide.

energy caused by ischemia causes an influx of calcium as well as a decomposition of cell membranes caused by free radical activation. When this breakdown occurs, glycerol is released into the interstitial fluid. This mechanism is supported by laboratory studies that show that glycerol generation occurs in proportion to free radical production in the tissues.[23] Thus, glycerol is an important marker of cell membrane damage. The glutamatergic system is also an important mediator for inducing excitotoxic damage in TBI. With brain injury, presynaptic glutamate secretion induces excitotoxicity and an increase in the influx of Ca2+ through *N*-methyl-D-aspartate (NMDA) receptors.[24] Thus, the glutamate measurements can aid in the evaluation of excitotoxicity after injury.[25]

CURRENT GUIDELINES FOR CLINICAL APPLICATION

As MD gained favor among intensive care doctors, a consensus meeting was held in 2002 to determine its use. The recommendations included[15] that:

1. This procedure is clinically indicated in aneurismal SAH and severe TBI.
2. The catheter should be placed in the tissue at risk (pericontusional tissues, right frontal in diffuse axonal injury, and within the distribution of vessels at risk for vasospasm) and an additional catheter should be place in CT normal-appearing tissue in patients with TBI.
3. All values are unreliable for the first hour after insertion.
4. Glutamate and the LPR are reliable markers of ischemia.
5. MD may assist with targeted therapy to prevent secondary ischemia.

MD IN TBI

Molecular Trends in TBI

MD has a multitude of research and clinical uses in TBI and, at present, the most common patient care indication is avoiding secondary injury. In TBI, ischemia after the primary injury is common and may lead to metabolic derangements that are reflected by changes in extracellular concentrations of key molecules. Thus, under anaerobic conditions, a decrease in glucose to zero or near zero, an increase in lactate, and an increase in the LPR to more than 20 to 30 is expected. If this ischemic pattern is detected before irreversible damage, interventions such as increasing inspired oxygen or decreasing ICP may help salvage vulnerable tissue and improve patient outcomes.

To test whether these alterations in glucose, lactate, and glutamate concentrations would accompany ischemia, Hlatky and colleagues[26] placed both $Pbto_2$ probes and MD catheters in patients with severe TBI. They analyzed the MD findings when the Pbo_2 probe indicated that ischemia was present (<10 mm Hg), and, as expected, the dialysate glucose significantly decreased, whereas the lactate, LPR, and glutamate increased under these hypoxic conditions. In addition, Belli and colleagues[27] explored the relationship between MD patterns and increases in ICP in 25 patients and showed that an LPR greater than 25 or a glycerol level greater than 100 μmol/L with a normal ICP strongly predicted an increase in ICP within 3 hours. Thus, if trends toward ischemia are noted, maneuvers to increase cerebral perfusion and decrease ICP may be instituted.

Several studies have attempted to identify critical substrate values that predict a poor outcome, and thus, if interventions could reverse the progression toward these critical values, the patient outcome may improve. Paraforou and colleagues[28] compared the MD results in 34 patients with severe TBI and found that all favorable outcome patients had LPRs less than 37 and glycerol levels less than 72 mmol/L. These findings raise the possibility of cutoff values similar to ICP, cerebral perfusion pressure (CPP), and $Pbto_2$. However, at present, no study has found that interventions directly based on MD results improve patient outcomes. This may be because a single MD probe may only show changes in a small region of brain, whereas patient outcome depends on whole-brain changes. Thus, it is important to specify a detailed probe location when interpreting the literature concerning brain MD. Perhaps combining data sets from many of the centers that use MD worldwide could yield sufficient statistical power to achieve this aim.[15]

Outcome Prediction in TBI

After multiple animal and human studies verified the ability of MD to reliably detect ischemic and other putatively harmful neurochemical trends in TBI, investigators attempted to determine whether metabolic derangements recorded with MD could predict outcome. Goodman and colleagues[29] and other investigators reported that in severe patients with TBI, the median lactate level and the lactate-glucose ratio were statistically significantly higher in patients who died.[30] Chamoun and colleagues[31] studied glutamate levels in 165 patients with severe TBI and identified 2 distinct patterns. In pattern 1, the glutamate normalized over time (started low and remained low or started high

and decreased over time), and, in pattern 2, the glutamate increased over time or remained increased. The pattern 2 patients had a statistically significant higher mortality and poorer outcome compared with pattern 1.[25]

Low and colleagues[32] attempted to predict patient outcomes based on parameters such as time of admission, mean arterial pressure, ICP, CPP, $Pbto_2$ data, and MD results. These investigators found that the addition of MD to this model improved its predictive value from 78% to 90%, and this variable was even shown to improve the predictive value more than $Pbto_2$ data.

Bullock and colleagues[25] initially developed an ischemia score based on hypoxemia, hypotension, cerebral blood flow, herniation, and low CPP, and this score was negatively correlated with the Glasgow Outcome Score (GOS) at 3 months and 6 months. With the addition of MD, a statistically significant relationship between lactate and pyruvate and the ischemic score was found. A correlation of the lactate/glucose ratio and the 3-month outcome was also found.[33]

Understanding TBI

MD can also play a major research role in understanding the pathophysiologic mechanisms that accompany TBI. We have explored neuronal vulnerability using MD with cerebral vascular autoregulation measurements in patients with severe TBI. In 3470 MD samples from 25 patients, the cerebral extracellular biomarkers (glucose, lactate, pyruvate, glycerol, and glutamate) were measured. The calculated pressure reactivity index (PRx), ICP, and mean arterial pressure were used to estimate cerebral vascular autoregulation.

After injury, the extracellular glucose concentration decreased, and the levels of glycerol, glutamate, and LPR, which indicate cerebral ischemia and neural cell damage, increased. On the fourth day after injury, the extracellular glucose concentration improved, and the value of LPR decreased. Along with these trends, the average PRx decreased daily and became negative on the fifth day after injury (**Fig. 3**). These results suggest that cerebral vascular autoregulation, and thus the cerebral vulnerability, may recover on the fourth day after TBI.[34]

MD IN SAH

The outcome of patients with aneurismal SAH is determined by the primary injury from the aneurysm rupture as well as by the secondary injury from events such as vasospasm, which can compromise the cerebral blood flow and significantly affect metabolism.[35] Similar to TBI, an increased concentration of brain tissue lactate and an increased LPR could reflect ischemia, and, with early intervention, a reduction in permanent neurologic deficits from vasospasm may be possible.[36,37]

These metabolic derangements were verified by Schulz and colleagues,[38] who found lower levels of energy substrates, higher levels of lactate, and higher levels of neuronal injury markers in patients with severe and complete ischemia. Unterberg and colleagues[39] also showed that, with ischemia, glucose decreased by 64%, lactate increased by 112%, and glutamate increased approximately 400% compared with a normal extracellular environment.[40]

One important SAH study found that this ischemic metabolic pattern preceded the occurrence of a delayed ischemic neurologic deficit (DIND). In this study, the mean delay from the peak in the LPR to the occurrence of a DIND was 23 hours (range 4–50 hours) and the mean delay from the ischemic metabolic pattern to a DIND was 11 hours. These results had a sensitivity for prediction of a DIND of 94%, a specificity of 88%, and a positive predictive value of 85%. Thus, in the proper clinical setting, MD may predict the occurrence of a DIND and cerebral infarction an average of 11 hours before its clinical appearance.[41] Although these data need more generalized validation in multiple centers, no other method of neuromonitoring offers the potential to preemptively detect harmful events and trends in patients with both SAH and severe TBI.

Glutamate has also been shown to be increased in the extracellular fluid of patients with SAH after secondary insults. This increase may be caused by an increased release from neurons or a decreased reuptake by astrocytes from the synaptic cleft,[42] and may lead to neuronal injury and poor outcome.[43]

Invasive metabolic monitoring may thus help to select those patients who may benefit from measures such as endovascular intervention or decompressive hemicraniectomy by the early detection of critical vulnerability. Studies on the effect of intracranial hypertension in patients with SAH showed that 83% of patients who developed increased ICP had cerebral metabolic derangements before the first increase in ICP (LPR >25, glycerol >80 μmol/L, and glutamate >10 μmol/L for >6 hours).[44] The sensitivity of MD for detecting cerebral compromise in patients with SAH may be better than that of ICP and CPP monitoring because the LPR or $Pbto_2$ were abnormal in many instances when the ICP was initially normal and then increased.

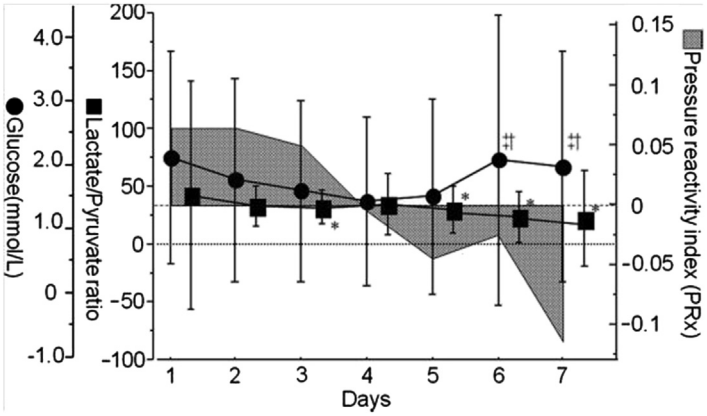

Fig. 3. The time course of biomarkers in 3470 microdialysates and PRx. The extracellular concentration of glucose decreased until day 4 and then increased until day 7. The daily average PRx decreased after day 1 and became negative after day 4. With improved cerebral pressure autoregulation, the extracellular glucose concentration increased, and LPR, which indicates tissue ischemia, decreased.

MOLECULES UNDER INVESTIGATION

In addition to the clinically available markers, many other molecules are currently being investigated for SAH and TBI. Mellergard and colleagues[45] reported the extracellular cerebral response of 2 of the most studied neurotrophic factors, fibroblast growth factor 2 (FGF2) and vascular endothelial growth factor (VEGF). The VEGF concentration was significantly higher in patients with TBI, whereas the FGF2 showed a tendency to be higher in patients with SAH. These data will assist in determining the inflammatory mechanism of injury and in identifying a potential threshold value for these chemokines for interventions as well as the possible timing of neural transplantation strategies.

Nitric oxide (NO) metabolite concentrations after SAH are another potential area of study. NO concentrations decreased on average by 21% in patients with SAH, which may lead to vasoconstriction and decreased local CBF.[46] Khaldi and colleagues[47] showed that brain tissue oxygen tension was strongly correlated with dialysate nitrate and nitrite, suggesting that substrate delivery and NO are linked in the pathophysiology of vasospasm after SAH.

Using 100-kDa MD probes, specific changes in certain protein concentrations occur approximately 4 days before the onset of symptomatic vasospasm. In particular, the protein concentrations of several isoforms of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were 1.79-fold higher in the patient group that later developed symptomatic vasospasm, whereas heat-shock cognate 71-kDa protein (HSP7C) isoforms were decreased to 0.50-fold. Thus, GAPDH and HSP7C may be used as early markers indicating the later development of symptomatic vasospasm after SAH.[48]

LIMITATIONS AND FUTURE DIRECTIONS

Although MD catheters have a multitude of uses, they have many drawbacks. The most limiting factor is the cost and labor-intensive nature of the collection and analytical systems despite the elegantly simple and robust pump and probes. This factor has restricted their widespread use throughout the neurointensive care community. Many samples are necessary for the acquisition of data and trends, and a qualified individual must spend time gathering and interpreting the results.[49] Also, many of the time-dependent changes in the 5 commonly used analytes are too complex for the current level of understanding, and thus cannot be translated into changes in patient care.

The limited volume of brain tissue sampled from the device is also a consideration. The current recommendation is to place the probe tip in pericontusional tissue in patients with TBI and the parent vessel territory in patients with SAH. Accurate placement can be difficult, and an aberrant probe position such as in the ventricle or outside the dura may render the data useless. In addition, the probes are delicate and cannot withstand pulling or head rotations unless carefully secured to the scalp, and inadvertent fracture of the membrane or disconnection from the pump preclude its use.[50]

In a series of 48 patients with MD probes, Stuart and colleagues[51] had 14 patients (29%) with catheter-related issues. These issues included

catheter dislodgement, malfunction of the micropump collection system, and failure of sample analysis by the computer system. The limitations include the complications from the invasive procedure, and, although the risk is small, intracranial hemorrhage and infections are possible but have not been reported in the literature.

There are a multitude of studies attempting to expand the clinical indications for MD. In particular, quantifiable assays of antibiotics, anticonvulsants, neuroprotectants, and chemotherapeutic agents hold promise for more accurate and effective central nervous system dose determination.[52,53] In addition, catheters with higher membrane permeability may assist in studies of inflammatory markers and their effects on the brain.[50] Another area of interest is the use of MD to determine a drug's effect on cerebral metabolism. In a study by Mazzeo and colleagues,[54] cyclosporine A was administered to patients with severe TBI, and the brain energy metabolism was measured. This study showed that brain glucose, lactate, and pyruvate were higher in the cyclosporine group compared with the control group, and the LPR was decreased in the cyclosporine group.

Another active research area is novel biomarkers. Investigators are attempting to identify new molecules with prognostic value within the blood and CSF, but MD offers a unique opportunity for monitoring the extracellular fluid for potential targets.

From a clinical standpoint, nearly every area of cerebral dysfunction has the potential to benefit from these devices by determining prognosis, effectiveness of an intervention, and pathophysiologic mechanism. In the literature, multiple investigators have described its use in pediatric head trauma, stroke, intracerebral hematoma, and general comatose patients.

MD studies in epilepsy have shown a large increase in glutamate in the hippocampus of epileptic patients during the onset of a seizure. Extracellular glutamate has also been found to be increased in the epileptogenic focus as well as the pathway of propagation.[55] In studies with liver failure, extracellular glutamine correlated with the LPR as well as ICP. Thus, with the assistance of MD, the mechanism for cerebral edema may be elucidated and targeted therapies may be developed.[56]

Neuroanatomy and physiology also benefit from the use of MD. Fried and colleagues[57] placed MD catheters into epileptic patients in conjunction with depth electrodes and discovered that extracellular dopamine in the human amygdala increased with reading, memory, and learning. In patients who quickly mastered a task, the dopamine increased rapidly and slowly diminished, whereas the dopamine slowly increased in patients who required more time to gain experience. MD has a great potential impact on the study of both normal and pathologic processes.

SUMMARY

MD has yielded important results in neuromonitoring for neurologically compromised patients. This device allows the direct measurement of extracellular molecules in an attempt to characterize metabolic derangements before they become clinically relevant. Advancements in technology have allowed for the bedside assay of multiple markers of ischemia and dysfunction in energy production, and the applications for TBI and aneurismal SAH have been well established. As clinicians become more comfortable with these tools, their widespread use will increase and the potential for clinical impact will continue to increase. No other neuromonitoring technique has such potential at minimal cost in terms of invasiveness and risk to the patient.

Well-organized multicenter studies are needed to define new analyte biomarkers and to determine the threshold values of these analytes to suggest actions to be taken in the patient. Only on this basis can a rational study be designed to determine whether use of MD can improve patient outcome, which is the ultimate goal of the neurointensivist.

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