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Microdialysis: Is it ready for prime time?

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Abstract

Purpose of review—This review highlights recent advances in cerebral microdialysis for investigational and clinical neurochemical monitoring in patients with critical neurological conditions.

Recent findings—Use of microdialysis with other methods including positron emission tomography, electrophysiological monitoring and brain tissue oximetry in traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) with vasospasm, and infarction with refractory increased intracranial pressure have been reported. Potentially adverse neurochemical effects of nonconvulsive status epilepticus and cortical slow depolarization waves both of which are increasingly recognized in TBI and stroke patients have been reported. The explosive growth in the use of cerebral oximetry with targeted management of brain tissue oxygen levels is leading to greater understanding of derangements of cerebral bioenergetics in the critically ill brain, but there remain unresolved basic issues. Understanding of the analytes that are measurable at the bedside – glucose, lactate, pyruvate, glutamate and glycerol – continues to evolve with glucose, lactate, pyruvate and the lactate/pyruvate (L/P) ratio taking center stage. Analytes including inflammatory biomarkers such as cytokines and metabolites of nitric oxide are presently investigational, but hold promise for future application in advancing our understanding of basic pathophysiology, therapeutic target selection and prognostication. Growing consensus on indications for use of clinical microdialysis and advances in commercially available equipment continue to make microdialysis increasingly “ready for prime time.”

Summary—Cerebral microdialysis is an established tool for neurochemical research in the intensive care unit. This technique cannot be fruitfully used in isolation, but when combined with other monitoring methods provides unique insights into the biochemical and physiological derangements in the injured brain.

Keywords

brain injury; neurochemical monitoring; microdialysis; traumatic brain injury; subarachnoid hemorrhage

Introduction

Cerebral microdialysis was introduced for basic studies almost 40 years ago and has been used clinically for neurochemical monitoring in the intensive care unit since 1992[1,2].

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Several excellent reviews have appeared in recent years [••3–18]. Some are definitive and detailed while others are more terse but accessible and informative. In addition, a comprehensive handbook of microdialysis has been published[••19]. Cerebral microdialysis was last reviewed in this journal in 2006 [••20], and the purpose of the current communication is to review and synthesize new contributions on microdialysis in acute brain injury predominantly from 2007 through 2008 with some consideration of this technique's readiness for routine application in the intensive care unit.

Neurochemical mechanisms of acute brain injury studied using microdialysis

Microdialysis analytes available at the bedside can provide information about brain bioenergetics, excitatory amino acid release, and membrane integrity[3–6,9,11–14,17,21–25]. Glucose, pyruvate and lactate measurements provide information about the relative contributions of aerobic and anaerobic metabolism to bioenergetics. Glutamate measurement provides insight into the excitatory amino acid milieu of the brain and since amino acids are released uncontrollably during energy failure, this amino acid also serves as a marker of bioenergetic insufficiency. Glycerol is released by the enzymatic cleavage of cellular membrane triglycerides and indicates cellular distress including energy failure. In the past two years, microdialysis work has emerged defining the range of bioenergetic disturbances in acute brain injury, the contribution of cortical electrical disturbances including non-convulsive status epilepticus and cortical spreading depolarizations to neurchemical distress, and several novel analytes with translational potential have been investigated.

Bioenergetics can be evaluated by examining the availability of fuel – glucose – that may be metabolized aerobically in the tricarboxylic acid cycle to produce carbon dioxide and water with a high adenosine triphosphate (ATP) yield. Alternatively, glucose may be metabolized anaerobically via glycolysis to produce lactate with a miserable ATP yield. Pyruvate is at the terminus of glycolysis and at the entry point of the tricarboxylic acid cycle. Lactate concentration elevation and elevation of the lactate/pyruvate (L/P) ratio are robust and reliable indicators of increased anaerobic metabolism. A shift to anaerobic metabolism may result from ischemia or hypoxia where the substrates necessary to sustain aerobic metabolism are simply not available or when there is failure of mitochondria oxidative phosphorylation. Ischemia has been well documented in TBI with an adverse impact of morbidity and mortality [26,27]. Ischemia may occur due to inadequate CPP, increased ICP or systemic disorders leading to inadequate perfusion, ventilation or oxygen carrying capacity[28]. Episodes of ischemia can be documented using microdialysis and the quantitative impact on bioenergetics measured [3,9,11,12,29–59]. Many investigators have shown that the tissue at greatest risk (and with the greatest potential for salvage) is the peri-contusional tissue in TBI and vascular territory in SAH. Probes placed directly in contusions or infarcts reveal severe neurochemical alterations indicative of irreversible damage. If a discrete lesion is not present, probe placement in a relatively silent region such as the right frontal lobe, can provide insight into cerebral bioenergetics.

In acute brain injury, bioenergetic pertubations characterized by diminished pyruvate concentration without hypoxia leading to an elevated L/P ratio as been described[••57,60]. This form of "non-ischemic" elevated L/P ratio has been designated type 2 elevation while conventional ischemic elevation is type 1[20]. This neurochemical anomaly may reflect impairment of the glycolytic pathway itself or inadequate availability or entry of glucose into the pathway possible due to shunting of glucose to competing pathways such as the pentose phosphate pathway that has been described in clinical TBI[•61]. Such decreased metabolic flux through the glycolytic pathway compromises both anerobic and aerobic metabolism, and may pose a bioenergetic threat to the brain. Regardless of mechanism,

decreased glucose concentration in microdialysate samples is a poor prognostic indicator [••62].

Generalized convulsive seizures are recognizable in the ICU, however, the high frequency of non-convulsive seizures and non-convulsive status epilepticus was not recognized until recently using continuous electroencephalographic monitoring. These seizures are associated with elevated L/P ratios and increased intracranial pressure [57,•63,••64]. This may be a situation in which increased tissue energy demand may not be adequately met. Seizure recognition and control as well as hypothermia would reduce metabolic demand.

Another electrical disturbance receiving increased attention is cortical spreading depolarization (CSD). First described in 1944 by Leão, these waves of cortical depolarization spread across the cortical surface at 2–3 mm/minute with immediately after-following hyperemia. The human neocortex was thought to be resistant to this phenomenon, but recent work in migraine, TBI and stroke has established CSD as a common and potentially pathogenic occurrence[••65–69]. CSD occurs in up to 50% of patients with severe TBI and 50–70% of patients with infarcts. Neurochemical events accompanying CSD have been studied using rapid sequence microdialysis (rsMD) that is an investigational technique using on-line flow injection analysis of glucose and lactate over a time scale of seconds representing a major improvement in temporal resolution over conventional microdialysis. In a series of elegant papers, rsMD as demonstrated marked glucose depletion and lactate elevation occurring in the hyperemic phase of CSD's. The severity of glucose depletion is proportional to the number of depolarizations and the authors propose that a visous cycle may be initiated in which CSD's lead to glucose depletion and bioenergetic distress which may beget additional depolarization waves [••70–72].

Novel analytes have recently received increased attention including cytokines, nitric oxide metabolites and N-acetylaspartate (NAA). Cytokines are proteins that exert a broad range of physiological effects. An individual cytokine may have multiple effects but generally these compounds are either pro-inflammatory or anti-inflammatory. The eventual inflammatory state of the tissue depends of the complex interplay of multiple cytokines. Initial studies were performed in serum and cerebrospinal fluid, but cytokines have now been measured in microdialysates in animals and humans [•73–77]. In Hillman's study, paired intracerebral microdialysis catheters with high-cutoff membranes were inserted in 14 comatose patients with subarachnoidal hemorrhage or TBI. Macroscopic tissue injury was strongly linked to IL-6 but not IL- lb activation, and IL release appeared to be stimulated by local ischemia. Hutchinson studied 15 TBI patients and found no significant relationships between IL-1 alpha and beta, IL-1 receptor (IL-1ra) and energy-related molecules. There was a significant correlation between increasing IL-1beta and increasing IL-1ra, and increasing IL-1ra with decreasing intracranial pressure. High concentrations of IL-1ra and high IL-1ra/IL-1beta ratio were associated with better outcome. Mellergard and colleagues measured the concentration of interleukin (IL)-1 beta, IL-6, IL-8, macrophage inflammatory protein-1 beta, regulated on activation, normal T-cell expressed and secreted (RANTES), fibroblast growth factor-2, and vascular endothelial growth factor was determined by a multiplex assay, and IL-10 was determined by enzyme-linked immunosorbent assay in 38 patients.

Nitrate and nitrite are the oxidative metabolites (NOx) of nitric oxide (NO), a gaseous neurotransmitter that contributes to regulation of vascular tone, neuronal communication and inflammation. NO may be helpful in acute brain injury by maintaining cerebrovascular reactivity but at higher concentrations such as those seen in inflammation could be detrimental; therefore, measurement of NOx has received attention. Low NOx concentrations correlate with decreased cerebral blood flow, diminished cerebrovascular

reactivity and poor outcome in TBI and SAH [78–81]. Instrumentation suitable for NOx measurement in the ICU is available but is not widely used in neurocritical care.

N-Acetylaspartate (NAA) is a neuronal marker present in high concentration in the CNS that can be measured by proton magnetic resonance spectroscopy and NAA depletion is a marker of neuronal damage and death. Belli and colleagues investigated 19 patients with TBI using microdialysis to recover NAA, lactate, pyruvate, glycerol and glutamate, and showed that NAA was 34% lower in non-survivors[82]. A non-recoverable fall in NAA was observed in non-survivors beyond day 4 with a concomitant rise in lactate-pyruvate ratio and glycerol suggesting bioenergetic failure contributed to the poor outcome.

Does microdialysis have a role in clinical decision-making in the critical care unit?

Microdialysis is one of several techniques used in monitoring the critically ill patient. In order to impact clinical decision making, monitoring should allow detection of pathophysiological events, provide guidance so that targeted therapy can be deployed and allow assessment of effects of therapy. Monitoring may also provide prognostic information that may guide decisions about the appropriate intensity and duration of therapy.

Glycerol results from the enzymatic degradation of membrane triglycerides and indicators loss of cellular structural integrity. [83–87]. Belli et al reported that a L/P ratio >25 and glycerol >100 micromole/L, were associated with significantly higher risk of imminent intracranial hypertension, but glutamate >12 micromole/L was not predictive. An abnormal L/P ratio was predictive of an ICP rise above normal levels in 89% of cases. These changes occurred before the onset of intracranial hypertension, suggesting that biochemical impairment may occur before low cerebral perfusion pressure is detectable; therefore, L/P ratio and glycerol elevations may be early warning signals of imminent deterioration [•88].

Glutamate, the major excitatory amino acid in the brain, is critical for physiological signaling and long-term potentiation. Uncontrolled release is seen in experimental and clinical TBI and ischemia, but this biomarker may be a relatively late indicator of dysfunction and has not been a major focus of investigation in the past two years. Astrocytic uptake keeps brain interstitial glutamate levels low. Astrocytes convert glutamate to glutamine that is released and reconverted to glutamate in neurons. This cycle is energy demanding and impaired energy metabolism may lead to low interstitial glutamine/glutamate ratios. Using microdialysis measurements from noninjured cortex in 33 patients with SAH, investigators found lactate/pyruvate (L/P) ratios correlated to the glutamine/glutamate ratios but the correlation was no stronger than the correlation between L/P or lactate and glutamate alone. During periods of bioenergetic crisis indicated by L/P ratios above 40 there were high interstitial glutamate levels. In periods with L/P ratios above 40 with low pyruvate levels, interstitial glutamine levels were decreased, suggesting ischemia and failing astrocytic glutamine synthesis. Periods with L/P ratios above 40 and normal or high pyruvate levels were associated with increased glutamine levels, possibly indicating an astrocytic hyperglycolytic response to high interstitial glutamate levels. Moderately elevated L/P ratios cannot always be interpreted as failing energy metabolism, and pyruvate levels may discriminate whether or not there is sufficient astrocytic capacity for glutamate/glutamine cycling in the brain [••89]. While general ICU patients experience reduced mortality and morbidity when nutritionally supplemented with intravenous glutamine, there has been reluctance to use glutamine supplementation in neurosurgical patients for fear of elevating intracerebral glutamate levels. Berg el al studied 15 TBI patients receiving glutamine infusions that increased plasma glutamine concentration by 30%, but no plasma or intracerebral glutamate were observed, suggesting this nutritional supplementation may

be an option in the neurointensive care [90]. Miller et al studied interstitial glutamate in intracerebral hemorrhage (ICH) in12 consecutive patients undergoing Frameless Stereotactic Aspiration and Thrombolysis (FAST) of deep ICH's. Glucose, lactate, pyruvate, and glutamate were measured in the perihematomal tissue of patients undergoing minimally invasive hematoma evacuation. Brain hematoma volumes were reduced 87% during FAST and National Institute of Health Stroke Scale (NIHSS) scores were improved from an average of 19 at admission to 12.6 at time of discharge. Glutamate average values decreased from the first 24 hours of measurement (12 mmol/L +/− 6) to the final 24-hour epoch (5 mmol/L +/− 6). Ischemic L/P ratios were not found in peri-hematomal regions and were unchanged during hematoma drainage. The authors suggest that excitotoxicity related to glutamate may have an important impact in ICH, but that ischemia may have little role in secondary peri-hematomal damage [•91].

Many experimental studies have demonstrated improvement in microdialysate neurochemical parameters with hypothermia and several series have been reported in critically ill patients [31,42,92–97]. Berger reported an open, prospective observational study in 24 patients with large MCA infarction undergoing either hypothermia (33 degrees C), hemicraniectomy, or maximum conservative therapy with probe placement in the peri-infarct tissue within 24 hour after stroke onset. Glutamate concentrations in patients treated with hemicraniectomy (5.3 +/− 0.5 mumol) and hypothermia (14.5 +/− 3.6 mumol/l) were significantly lower than in conservatively treated patients (68.3 +/− 5.2 mumol/l). Glycerol concentrations were lower in patients treated by hypothermia (111 +/− 17 mumol/l) and hemicraniectomy (138 +/− 8 mumol/l) compared to conservatively treated patients with 612 +/− 27 mumol/l. The lactate-pyruvate ratio was lower both in the hypothermia (16.2 +/− 3.3) and hemicraniectomy groups (31.3 +/− 1.5) than in the conservative treatment group (56 +/− 2.9). Wang et al studied the effect of mild hypothermia on glucose metabolism and glycerol in 31 TBI patients with probes inserted into perilesional and normal brain tissue. In the hypothermia group, lactate/glucose ratio(L/G), lactate/pyruvate ratio(L/P) and glycerol in perilensional tissue were all decreased, and the L/P ratio in normal brain tissue was decreased. In normothermia, L/G, L/P and glycerol in perilensional tissue were higher than that in normal brain tissue. Mild hypothermia appears to protect brain tissues by decreasing L/G, L/P and glycerol in peri-lesional tissue and L/P in "normal brain" tissues. Bioenergetic crisis and membrane phospholipid degradation in peri-lensional tissue are impacted to a greater degree by hypothermia than derangements in normal cerebral tissue[87].

The increased use of cerebral oximetry and the demonstrated adverse impact of hypoxia on ICP, cerebral bioenergetics and outcome led to increased interest in hyperoxia in TBI. Tisdal and colleagues used brain tissue oxygen tension measurement, cerebral microdialysis, and near-infrared spectroscopy to study the effects of normobaric hyperoxia in 8 adults with TBI within the first 48 hours postinjury. Inspired oxygen at normobaric pressure was increased from baseline to 60% for 1 hour and then to 100% for 1 hour before being returned to baseline for 30 minutes. When inspired oxygen was 100%, brain tissue oxygen tension increased by 7.2 kPa, microdialysate lactate concentration decreased by 0.26 mmol/L, microdialysate L/P ration decreased by 1.6. No significant changes in intracranial pressure or arterial or microdialysate glucose concentration were seen [•98]. In contrast, Nortje et al studied eleven patients with severe TBI using microdialysis, brain tissue oximetry, and oxygen-15 positron emission tomography (15O-PET) during normoxia and hyperoxia (FiO2 increase of between 0.35 and 0.50). Hyperoxia increased mean PbO2 from 28 +/− 21 mm Hg to 57 +/− 47 mm Hg ($p = .015$). Microdialysate lactate and pyruvate were unchanged, but the lactate/pyruvate ratio showed a statistically significant reduction (34.1 +/− 9.5 vs. 32.5 +/− 9.0, $p = .018$), but the magnitude of reduction was small, and the authors concluded that its clinical significance was doubtful[••99]. In a recent review, Diringer suggests that

additional studies are appropriate but that routine clinical use of hyperoxia is not currently warranted particularly in view of potentially harmful effects of this therapy[••100].

Hyperglycemia has been shown in multiple studies to be an unfavorable prognostic indicator in TBI, stroke and sepsis resulting in interest in rigorous glycemic control using insulin in critically ill patients. Two important recent papers using cerebral microdialysis challenge the utility of "tight" glycemic control. Vespa et al in 2006 reported 14 patients treated with rigorous insulin therapy had a reduction in microdialysis glucose by 70% of baseline concentration compared with a 15% reduction in 33 patients treated with a more relaxed insulin protocol[101]. Additionally, intensive insulin therapy was associated with increased occurrence of elevated glutamate (38+/−37% vs. 10+/−17%), elevated lactate/pyruvate ratio (38+/−37% vs. 19+/−26%) and low glucose (26+/−17% vs. 11+/−15%). Mortality was similar in the intensive and loose insulin treatment groups. More ominously, in a study of ICU patients in which glycemic was "tight" (4.4–6.7 mmol/L [80–120 mg/dL]) vs. "intermediate" (6.8–10.0 mmol/L [121–180 mg/dL]) range, tight systemic glucose levels were associated with a greater prevalence of low cerebral microdialysis glucose (65% vs. 36%) and brain energy crisis (25% vs.17%) than intermediate levels. Adjusting for intracranial pressure and cerebral perfusion pressure, systemic glucose concentration and insulin dose independently predicted brain energy crisis. Cerebral microdialysis glucose was lower in nonsurvivors than in survivors and brain energy crisis was associated with increased mortality at hospital discharge [••102].

In an important study, Marcoux reported that the L/P ratio in the first 4 days after trauma to allowed prediction of frontal brain atrophy at 6 months after injury. The lactate/pyruvate ratio was elevated >40 after for 32 +/− 29% of the mean percent time of monitored. At 6 months, the percentage of time of elevated lactate/pyruvate ratio correlated with the degree of frontal lobe brain atrophy, but not with global brain atrophy. This predictive effect of lactate/pyruvate ratio was independent of patient age, Glasgow Coma Scale score, and volume of frontal lobe contusion [••103].

In 2004 a conference of clinical microdialysis experts was convened to reach consensus on the clinical indications for deployment of microdialysis [104]. This panel recommended that microdialysis be considered in TBI and SAH patients requiring ICP and CPP monitoring. The battery of glucose, pyruvate, lactate, glycerol and glutamate was recommended with use of the calculated L/P ratio. An important outcome of the meeting was consensus on the site of probe placement. In TBI, placement in peri-contusional at risk tissue, was recommended and if the option for placement of a second probe is available, that probe should be placed in normal tissue. It was agreed that placement directly into contusions was of no value. In cased of diffuse injury, probe placement should be in the right frontal lobe. In SAH, the probe should be placed in the parent vessel's territory. In 2008, another consensus conference was convened, this time of intensivists and emergency physicians rather than microdialysis experts. This panel was more conservative and did not give specific recommendations on use of clinical microdialysis while lamenting the absence of Class I trials demonstrating the utility of microdialysis while acknowledging the scientific validity of the technique[•105].

Advances in methodology

Several methodological advances have been made in the last two years. The practical implementation of microdialysis in the intensive care unit continues to be dependent on the introduction of commercially available instrumentation. The introduction of the CMA600 bedside analyzer markedly accelerated both investigational and clinical applications of microdialysis. The next generation instrument, the CMA ISCUS^{flex} was introduced in late

2008 (CMA/Microdialysis, Solona, Sweden). Like its predecessor, this instrument uses enzymatic reagents and colorimetric measurement, but is substantially smaller, has batch processing capability, and permits monitoring and time trend display of neurochemical data on up to eight patients. Glucose, pyruvate, lactate, glycerol, glutamate and urea are the available analytes. The same company has recently released software (ICUpilot) that allows interfacing with other monitoring equipment so that physiological and neurochemical data can be displayed on several commonly used ICU information systems. For several years, the primary commercially available brain microdialysis catheter was the CMA 70 Brain MD Catheter with a relatively low molecular weight cut-off, 20 kDa. The CMA 71 High Cut-Off Brain Microdialysis Catheter has a molecular weight range up to 100 kDa that is more suitable for sampling larger molecules such as cytokines. At present, CMA-71 probes are not FDA-approved and must be used under a research protocol in the US Modifications of the lower molecular weight cut-off probe are also available to facilitate use with cranial bolts that permit placement of multiple probes and sensors.

Conclusion

Cerebral microdialysis continues to provide substantial new information about the neurochemistry of the acutely injured brain. Mechanistic insights have already been translated to clinical application through increased attention to CPP, tissue oxygenation, vigilance for cortical electrical disturbances and judicious application of mild hypothermia. We can anticipate that use of microdialysis in clinical investigation will continue to provide valuable mechanistic information and therapeutic options. The “routine” application of microdialysis is within the reach of technically advanced intensive care units where this technique must be used in conjunction with other methods to provide true multi-modality monitoring of the critically ill patient.

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