

Advanced monitoring in traumatic brain injury: microdialysis

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Abstract

Purpose of review: Here we review the present state-of-the-art of microdialysis for monitoring patients with severe traumatic brain injury (TBI), highlighting the newest developments. Microdialysis has evolved in neurocritical care to become an established bedside monitoring modality that can reveal unique information on brain chemistry.

Recent findings: A major advance is recent consensus guidelines for microdialysis use and interpretation. Other advances include insight obtained from microdialysis into the complex, interlinked TBI pathologies of electrophysiological changes, white matter injury, inflammation and metabolism.

Summary: Microdialysis has matured into being a standard clinical monitoring modality that takes its place alongside intracranial pressure and brain tissue oxygen tension measurement in specialist neurocritical care centres, as well as being research tool able to shed light on brain metabolism, inflammation, therapeutic approaches, blood brain barrier transit and drug effects on downstream targets. Recent consensus on microdialysis monitoring is paving the way for improved neurocritical care protocols. Furthermore, there is scope for future improvements both in terms of the catheters and microdialysate analyser technology, which may further enhance its applicability.

Key words: traumatic brain injury (human), microdialysis, metabolism, inflammation, blood–brain barrier, multimodality monitoring.

Introduction

Traumatic brain injury (TBI) is the largest single cause of death in those aged under 40 years in the developed world (1). Survivors experience varying disabilities that are often life-long, with demands on carers and resources (2). After the ictus, the greatest clinical challenge is to limit secondary brain injury, when complex, dynamic changes occur in cerebral physiology and chemistry (3).

Hypotension, hypoxia, hypoglycaemia, sustained intracranial pressure (ICP) rises, seizures, and infections are avoided with the aim of maintaining adequate cerebral perfusion and preventing herniation syndromes (3). Most patients, both adult and paediatric, suffering a severe TBI, defined as a presenting Glasgow Coma Score (GCS) ≤ 8 , will be managed with the use of ICP monitoring and cerebral perfusion pressure (CPP) targeted therapy (4).

Target-driven therapy is essential to improve patient outcome (5, 6). Currently, we monitor ICP and brain tissue oxygen tension (P_{btO_2}) with “real-time” analyses, which allows us to respond rapidly to any dangerous changes in these parameters (7). This is complemented with the analysis of brain chemistry performed using microdialysis. A typical bedside multimodality monitoring setup is illustrated in Fig. 1. Introduced clinically during the 1990s, microdialysis enables continuous monitoring of tissue chemistry to study transplanted tissue, surgical grafts or most commonly brain injury. First described in 1974 (8), only during the late 1990s did microdialysis become more readily available for hospitals worldwide due to advancements in computing hardware (9). Since then, microdialysis has been extensively refined, and methodological variants introduced to improve monitoring of the injured brain.

Principle

The microdialysis catheter consists of two concentric tubes. The outer tube is connected to a syringe pump that delivers perfusion fluid. The perfusate flows through the external tube down to the tip, where the final 10 mm of the catheter consists of a semi-permeable dialysis membrane allowing bi-directional diffusion between the perfusate and the extracellular fluid of the brain parenchyma (10). The diffusion rate is driven by the chemical gradient across the dialysis membrane (9). The perfusate, now termed microdialysate, is extracted via the inner catheter to be analysed.

Clinical indication

Indications for clinical monitoring using microdialysis are not clear-cut, younger patients generally have better outcome, nevertheless, caution should be maintained when selecting candidates (11*). It is generally accepted that patients with brainstem injury and central herniation should be excluded from the procedure because of the pre-disposition to poor outcome with such features (12). The post-resuscitation GCS is perhaps the most accurate assessment (13). Disease-specific recommendations have been identified in the most recent consensus statement (11*). In TBI microdialysis can be used to monitor “healthy” tissue (e.g. to guide systemic glucose treatment) and/or to monitor focal regions at risk. Similarly, in another form of acute brain injury, guidance in subarachnoid haemorrhage (SAH) suggests microdialysis as a primary monitoring device in mechanically ventilated (‘poor-

grade') patients or to monitor patients at risk of a secondary neurological deterioration (e.g. delayed ischaemic deficit) (11*).

Surgical procedure

The clinical microdialysis catheter is carefully placed within the cerebral parenchyma either via a cranial access device ("bolt") or tunnelled via a twist drill hole or placed under direct vision at craniotomy (14). The microdialysis catheter tip contains gold, visible on CT scan.

In TBI, insertion is guided by the type of injury sustained. In diffuse axonal injury, the catheter should be inserted in the non-dominant frontal lobe. In focal injury (acute subdural haematoma or contusion) the catheter should be placed in ipsilateral to the lesion in radiographically normal brain where possible. It is acceptable to place bilateral microdialysis catheters where focal injury results in significantly radiographically different brain (11*).

In SAH, the recommendation is to insert the microdialysis catheter in the watershed anterior cerebral artery–middle cerebral artery territory ipsilateral to the maximal blood load seen on CT or the ruptured aneurysm (11*). If the blood load is symmetrical, insertion in the non-dominant hemisphere is recommended. However, in delayed ischemic deficit, microdialysis catheters should be placed in tissue most at risk as directed by radiological findings (11*).

Understanding brain chemistry through microdialysis

The primary physical injury in TBI caused by impact is followed over the ensuing hours and days by complex pathology intertwining intracranial dynamics, electrophysiological responses, cerebral metabolism and inflammation. Modern neurocritical care means that gross ischaemia is usually avoided. However, despite seemingly adequate provision of metabolic fuels and oxygen, the injured brain sometimes cannot utilise them efficiently: termed 'mitochondrial dysfunction', and, in severe form, 'metabolic crisis', the exact basis is still not understood. A few recent studies have notably tied together brain extracellular focal chemistry with other brain measures in TBI patients, as follows.

Electrophysiological changes

Electrophysiological responses to TBI include cortical spreading depolarizations (CSD) associated with marked changes in glucose and lactate levels in the brain extracellular fluid (15). These can be regarded as waves of "bad chemistry" propagating spatially and temporally, often across large regions of the brain and/or around contusions. Another electrophysiological response found in TBI, and apparently related to CSD, are seizures (16) - typically non-convulsive seizures and periodic discharges (PD). Vespa and colleagues have built on their earlier work, and have now positively established linkage between seizures and metabolic crises (17**). Electrophysiological disturbances may go undetected unless patients are monitored continuously with electrodes. Depth electrodes inserted into the brain were more useful than scalp electrodes for monitoring seizures and PDs in TBI patients (17**). Seizures or PDs occurred in 61% of 34 subjects, with 42.9% of these seizures noted only on intracortical depth electroencephalogram (dEEG) and in some cases lasting for many

hours. Metabolic crisis as measured by elevated cerebral microdialysis lactate/pyruvate ratio (LPR) occurred during seizures or PDs but not during electrically non-epileptic epochs. PDs and seizures occurred in normal-appearing tissue at a similar rate to that of pericontusional tissue. This suggests that multiple regions of the brain are at risk for electrical instability, not just the pericontusional tissue recognised previously. The study has highlighted the importance of PDs hitherto often regarded as benign by electroencephalographers. Vespa et al. have suggested that both PDs and seizures are potential therapeutic targets in severe TBI. They described the seizures/PDs and metabolic crisis (elevated LPR) as being “time-locked”, a finding subject to the constraint that microdialysate collection vials were changed and analysed hourly whereas the EEG sampling rate was 2.5 kHz. Thus, there is no information yet on whether there is a cause-effect relationship between electrophysiology and metabolism (or *vice-versa*), or whether they are mutually interactive, or both results of some other initiating effect.

White matter injury

White matter, which is composed chiefly of glia, and constitutes the largest proportion of the brain, provides a vital support infrastructure for grey matter neurons. Magnoni et al. (18**) reported that microdialysis measurements of the axonal cytoskeletal protein tau in the brain extracellular space correlated well with diffusion tensor magnetic resonance imaging (DTI)-based measurements of reduced brain white matter integrity in the 1-cm radius white matter-masked region near the microdialysis catheter insertion sites. They found a significant inverse correlation between microdialysate levels of tau 13–36h after injury and fractional anisotropy (FA) reductions in comparison with healthy controls. FA

reductions near microdialysis catheter insertion sites were highly correlated with FA reductions in multiple additional white matter regions. Both microdialysis tau measurements and magnetic resonance DTI may reflect traumatic axonal injury. Perhaps surprisingly, there were no significant correlations between FA reductions and brain microdialysate metabolic markers (glucose, lactate, LPR and glutamate) and none between FA reductions and microdialysate amyloid-beta. No correlation was observed between other DTI parameters (mean diffusivity, axial diffusivity, radial diffusivity) and microdialysate tau or amyloid-beta.

Measuring biochemical pathways

Two recent ^{13}C -labelled microdialysis studies (19, 20*) have revealed insight into TBI patients' brain chemistry. The studies employed microdialysis perfusion with respectively 1,2- $^{13}\text{C}_2$ glucose (19) and 2,3- $^{13}\text{C}_2$ succinate (20*) with simultaneous collection of the products via the same catheters, with high-resolution ^{13}C NMR analysis. The first study (19), using 1,2- $^{13}\text{C}_2$ glucose, revealed that the major pathway, glycolytic lactate production (labelling pattern 2,3- $^{13}\text{C}_2$ lactate), was significantly greater in TBI brain than in normal brain. The minor pathway, pentose phosphate (PPP)-derived lactate production (3- ^{13}C lactate), was statistically not significantly different in TBI brain than in normal brain. However, several of the TBI individuals showed PPP-derived lactate elevation above the range observed in the normal brain. There was a shift in glucose metabolism from glycolysis towards PPP with decreasing PbtO_2 although glycolysis always remained dominant. The findings raise interesting questions about the roles of the PPP and glycolysis after TBI, and whether they can be manipulated to enhance the potentially reparative and antioxidant role

of the PPP for better patient outcome. The second study (20*), using 2,3-¹³C₂ succinate (disodium salt), showed that this molecule was metabolised via the TCA cycle (evidenced by ¹³C-labelling patterns in metabolites) and ameliorated cellular metabolism (evidenced by lowering LPR), proof-of-concept that the TCA cycle can be directly supplemented and TBI brain chemistry potentiated. Succinate is a tricarboxylic acid (TCA) cycle intermediate that interacts directly with complex II of the mitochondrial electron transport chain (ETC), enabling a 'shortcut' route (missing out ETC complex I) for oxidative metabolism. Lower LPR suggests that succinate improves redox balance, conceivably by boosting shuttles utilising mitochondrial ETCs to recycle NADH to NAD⁺, possibly promoting glucose utilisation and glutamate clearance from the interstitium, further supported by the finding of lower microdialysate concentrations of glucose and glutamate.

Neuroinflammation and blood-brain barrier

Microdialysis can provide unique information for clinical trials, establishing whether systemically administered drugs cross the blood-brain barrier, and informing on downstream targets and biomarkers. In TBI patients with diffuse injury, subcutaneous administration of human interleukin receptor antagonist (IL-1ra), in recombinant form as the pharmaceutical anakinra/Kineret, resulted in marked elevation of both circulating IL-1ra and brain extracellular IL-1ra (21). Alongside IL-1ra, other cytokines, chemokines and growth factors were analysed in a 42-plex Luminex assay (42 analytes) in 10 treated patients plus 10 control patients (without anakinra) (21). Multivariate (partial least squares discriminant) analysis of this dataset has recently revealed a pattern of response that questions the

simple classification of IL1ra as an 'anti-inflammatory' cytokine and highlights the importance of the microglial response to injury (22*).

A paired microdialysis catheter study (23) of peri-contusional vs. radiologically "normal" sites, measuring matrix metalloproteinases (MMPs), has shown that MMP-9 concentrations are increased in peri-contusional brain early post-TBI (within 72h) and potentially represent a therapeutic target to reduce haemorrhagic progression and vasogenic oedema.

Significance of lactate

The significance and roles of lactate in the brain are still debated. Microdialysis can provide insight. High brain LPR suggests high reliance on glycolysis, which can be due to ischaemia, in which case lactate is high and pyruvate is low, together with low glucose and (if measured) low PbtO₂. This is termed Type I LPR elevation. Alternatively, high lactate accompanied by less drastically lowered pyruvate, in the absence of ischaemia, is Type 2 LPR elevation, more often seen in TBI patients than Type 1 (24, 25). Significantly, transitions can occur within-patient between ischaemia-pattern and mitochondrial dysfunction-pattern (and *vice-versa*), with time post-injury, and that in the transition from ischaemia-pattern to mitochondrial dysfunction, pyruvate can rise with time (25).

Labelling studies have shown that lactate can be oxidatively metabolised *in vivo* by rat brain (26) and by human brain – both healthy (27, 28) and TBI (29). Debate still exists on the astrocyte-neuron lactate shuttle (ANLS) hypothesis (30, 31) about whether astrocyte glycolysis-derived lactate is the preferred energy substrate for neurons, or whether both

astrocytes and neurons independently metabolise glucose *per* their needs. Supporting the “independent model” is a kinetic metabolic modelling study in rats (32). Debate also exists (33) on the suitability of administering exogenous intravenous lactate as therapy for TBI (34-36).

Microdialysis guidance of therapy

Microdialysis is a valuable source of clinical information to assist evaluation of putative TBI therapies. Retrospective data analysis from 36 TBI patients showed normobaric hyperoxia association with increased excitotoxicity, evidenced by increases in microdialysate glutamate concentration with increasing fraction of inspired oxygen (37). Brain multimodal monitoring—including ICP, PbtO₂, and microdialysis—was more accurate than ICP monitoring alone in detecting cerebral hypoperfusion in a study of 27 patients with severe TBI and predominantly diffuse injury (38).

Future prospects

Microdialysis is a standard part of neurocritical care monitoring for severe TBI in some centres, in addition to its key role in clinical research studies. Besides adults, it is being extended to monitor paediatric severe TBI patients (39). Next steps will be to use microdialysis more consistently to inform patient management and therapy. The fundamentals for this have been set out in a recent Consensus Statement (11*) from microdialysis experts worldwide. The next stage is establishing a suitably tiered formal protocol for enabling microdialysis results to be optimally utilised alongside intracranial

pressure (ICP) monitoring and other modalities, to inform decisions on individualised therapy for each patient. PbtO₂ probes are desirable in this multimodal partnership, to help to differentiate hypoxia/ischaemia from mitochondrial dysfunction/metabolic crisis. Besides TBI, microdialysis has scope for increased use in monitoring other forms of acute brain injury, e.g. SAH (36).

In injured brain, electrophysiological disturbances have emerged as important elements within the adverse metabolic changes that are linked to poor functional outcomes. However continuous electrophysiological measurements are hard to implement. Technological improvement and/or understanding of appropriate surrogate markers would be potentially beneficial.

Faster brain microdialysis measurement on-line rather than the present hourly vial changes is desirable, as electrophysiological changes can induce potentially damaging rapid changes in brain chemistry. These early warning signs will be missed on hourly measurements, thereby losing an opportunity for therapy. Progress on on-line detectors has been made in a research context, reported microdialysis measures are as yet confined to potassium, glucose and lactate, but not pyruvate (40). Online, rapid detection of key metabolites in an easy-to-use, robust, compact, low-cost format would be beneficial and would potentially encourage adoption of microdialysis by more centres.

While both 20 kDa and 100 kDa clinical catheters allow recovery of extracellular small molecules (metabolites), the 100 kDa additionally permits recovery of many water-soluble extracellular proteins, e.g. cytokines and chemokines. Inflammation is a crucial aspect of the

response to TBI. However, optimising microdialysis recovery of proteins remains a work-in-progress. Success using human serum albumin (HAS) supplementation of the microdialysis perfusion fluid (21, 41, 42) is nowadays becoming unfeasible as increasing licensing restrictions on pharmacy manufacturing mean that formulation with this blood product is, depending on the pharmacy, either not permitted or prohibitively expensive. Dextran is an alternative being explored (43, 44); it is a polysaccharide with various polymer sizes, and not a protein. Serum albumin is widely utilised in biochemistry (not just microdialysis) as an agent for blocking nonspecific binding losses of proteins of interest that would otherwise be variably trapped by adherence to surfaces in tubing, artificial membranes, vials etc. Whether dextran, which was introduced to microdialysis primarily as a fluid-balancing osmotic agent, can prevent nonspecific binding of proteins, remains to be established. Another approach to improving catheter technology is coating it with Pluronic (a.k.a. Poloxamer) (44, 45), aimed to reduce protein binding and inhibit biofouling and encapsulation. Pluronic coating is only reported experimentally, and whether this might represent any significant improvement on current microdialysis technology and subsequent progress to clinical adoption, are future questions.

Conclusions

Microdialysis has matured into a standard clinical monitoring modality (alongside ICP and PbtO₂) in specialist neurocritical care centres as well a research tool for shedding light on brain metabolism, inflammation, therapeutic approaches, blood brain barrier transit and drug effects on downstream targets. Recent consensus on microdialysis monitoring paves the way for improved neurocritical care protocols. Scope exists for future improvements

both in terms of the catheters and microdialysate analyser technology, which may further enhance applicability.

Key points:

- Traumatic brain injury (TBI) is the largest single cause of death in those aged under 40 years in the developed world, and after the ictus, the greatest clinical challenge is to optimise patient outcome by limiting secondary brain injury, when complex, dynamic changes occur in cerebral physiology and chemistry.
- Microdialysis has matured into a standard clinical monitoring modality alongside intracranial pressure and brain tissue oxygen tension monitoring in specialist neurocritical care centres.
- A recently published Consensus on microdialysis monitoring is paving the way for improved neurocritical care protocols and individualised patient therapy.
- Microdialysis is continuing to grow as a research tool for shedding light on brain metabolism, inflammation, therapeutic approaches, blood brain barrier transit and drug effects on downstream targets, and thus microdialysis provides important evidence in clinical trials.
- Scope exists for future improvements both in terms of the catheters and microdialysate analyser technology, which may further enhance applicability.

Disclosure

The author(s) declare the following potential conflict of interest with respect to the this article: PJH is a Director of Technicam, which manufactures a triple lumen cranial access

device used for microdialysis catheter insertion. The other authors (KLHC and AY) have no conflict of interest regarding this article.

Figure legend

Figure 1. Bedside multimodality setup typically used in severe TBI neurocritical care, comprising monitors for intracranial pressure (ICP), brain tissue oxygen tension (PbtO₂) and microdialysis. Illustration copyright Susan Giorgi-Coll and reproduced here with her permission.

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