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UNDERSTANDING THE DISEASE

# Understanding and monitoring brain injury: the role of cerebral microdialysis

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## Introduction

Neurointensive care should focus on individualised therapy to limit secondary cerebral damage, i.e. the numerous pathogenic events (oedema, ischemia, impaired metabolism, seizures, excitoxicity, inflammation, etc.) taking place in the hours or days following acute brain injury (ABI) that may further aggravate outcome. Management using information from intracranial pressure (ICP) and cerebral perfusion pressure (CPP) monitoring remains an important focus of neurointensive care; however, this may be insufficient to determine optimal treatment strategies and to change patient prognosis [1]. Lack of effectiveness of therapy targeted to ICP/CPP may partly be because ICP monitoring fails to capture more complex secondary cerebral physiologic derangements that, if identified and effectively treated, could potentially improve outcomes. Cerebral microdialysis (CMD) allows a scrutiny of tissue biochemistry and enables clinicians to monitor the metabolic state of the injured brain [2]. Most attention has been directed towards patients with severe TBI (sTBI) and aneurysmal subarachnoid haemorrhage (aSAH). Protocols guided by CMD monitoring, in combination with ICP and other monitoring modalities (brain tissue $PO_2$, EEG), are therefore increasingly used. Such protocols have evolved from the recognition that microdialysis parameters relate to outcome [3] and that brain chemistry can be changed with therapy [4].

## Microdialysis monitoring

The CMD catheter is surgically inserted within the brain parenchyma (white matter), via a cranial access device (bolt), tunnelled via a twist drill hole or placed under direct vision at craniotomy. Catheter placement needs careful thought and may influence data interpretation. The exact area of insertion is directed by CT findings, generally in the non-dominant frontal lobe or ipsilateral to focal brain lesions (sTBI) or to the maximal blood load seen on CT in the parent aneurysm vessel territory or watershed anterior-middle cerebral artery territory (aSAH). The scope of CMD monitoring is multiple in neurointensive care (Fig. 1). It is a complementary technique for advanced bedside monitoring of severe ABI patients, namely those with post-resuscitation coma and abnormal CT lesions. It is also an essential clinical research tool to understand the complex pathophysiology of ABI and is evolving as potential tool to test novel therapeutic and drug effects in phase II physiology studies.

Several neurochemical markers (glucose, lactate, pyruvate, glutamate, glycerol) can be routinely sampled with CMD. The recent consensus guidelines on CMD monitoring recommend primarily using lactate/pyruvate ratio (LPR) and glucose as step 1 to guide clinical interventions. Data derived from CMD monitoring should be integrated with variables derived from other monitor modalities (mainly, ICP and brain tissue $PO_2$) [2]. Data interpretation depends on catheter location in normal appearing vs. lesioned brain regions. With this in mind, CMD is a valuable source of clinical information to assist in delivering individualised therapy to neurointensive care patients [5, 6]. It is uncertain whether therapy guided by CMD, in common with other monitors and interventions in ICU, contributes to better outcomes.

## Microdialysis as a clinical tool

### Monitoring of secondary ischemic insults

High CMD lactate levels are a marker of oxygen or substrate supply/demand mismatch [vasospasm, hypoxic/ischemic insults (decreased supply) or through fever, inflammation (increased demand)]. Inadequate flow/

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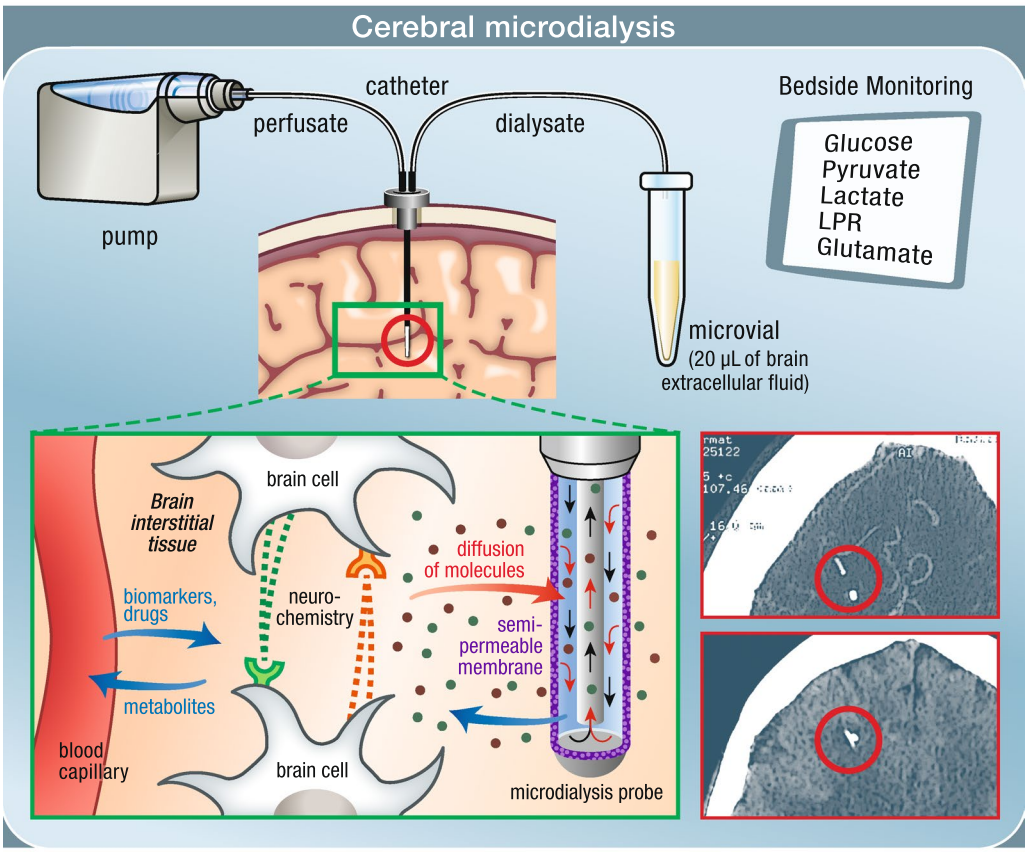


**Fig. 1** Bedside cerebral microdialysis monitoring. The microdialysis catheter consists of two concentric tubes. The outer tube is connected to a syringe pump that delivers perfusion fluid. The perfusate flows through the external tube down to the tip (red circle), where the final 10 mm of the catheter consists of a semipermeable dialysis membrane allowing bidirectional diffusion between the perfusate and the extracellular fluid of the brain parenchyma (subcortical white matter, as illustrated by head CT). The diffusion rate is driven by the chemical gradient across the dialysis membrane. The perfusate, now termed microdialysate, is sampled via the inner catheter in a 20-µL microvial, to be analysed (usually hourly) using a kinetic enzymatic analyser and displayed at the bedside for brain extracellular (interstitial tissue) concentrations of glucose, pyruvate, lactate, lactate/pyruvate ratio (LPR), and glutamate. At a standard 0.3 µL/min perfusate flow rate, the dialysate recovery is estimated to be ≈ 70% of actual brain concentrations. Consensus guidelines recommend to use primarily LPR and glucose as step 1 to guide clinical interventions. CMD monitoring data should be integrated with variables derived from other monitor modalities (ICP and brain $PO_2$). Low glucose (< 0.8 mmol/L = warning; < 0.2 mmol/L = critical) coupled with elevated LPR (> 25 warning; > 40 = critical) and low pyruvate (< 70 µmol/L) indicates ischemia (see [2] for reference values). Elevated LPR with normal-to-elevated (> 120 µmol/L) pyruvate suggests that impaired cerebral metabolism is related to other mechanisms than ischemia/hypoxia (e.g. hyperglycolysis, mitochondrial dysfunction). CMD monitoring is a complementary tool for advanced brain multimodal monitoring in neurointensive care. It is also an essential clinical research tool to study neurochemistry following ABI and as potential target to test novel therapeutic and drug effects in phase II physiology studies

oxygen supply generates anaerobic metabolism, high lactate with low pyruvate and therefore elevated to markedly elevated CMD LPR, usually coupled with low CMD glucose. Therefore, dynamic trends of L/P ratio and glucose can be used for bedside ischemia detection [5, 6].

However, CMD can also enable the differentiation of ischemic/hypoxic versus non-ischemic post-ABI mechanisms (such as aerobic hyperglycolysis or mitochondrial dysfunction) that also cause elevated CMD lactate and LPR (although generally to a lesser extent than ischemia/hypoxia) [2], with the potential to guide different treatment strategies.

## Monitoring of secondary non-ischemic insults

### *Energy dysfunction*

In the aftermath of ABI the brain's ability to use glucose as a fuel may be impaired, potentially leading to energetic failure and poor outcome. Keeping systemic glucose in the "moderate" range (6–8 mmol/L) and supporting the injured brain with rapid institution of enteral nutrition

is recommended [7]. Clinical investigation employing CMD catheter perfused with $^{13}C$-labelled substrates has revealed differences in metabolism between normal and injured brain and novel findings such as the uptake and metabolism of lactate [8]. This provides the rationale for novel approaches to therapeutic supplementation of cerebral metabolism, e.g. supplementing the injured brain with energetic substrates, such as lactate [9] or succinate [10]. In this setting, metabolic studies have exploited CMD biomarkers such as LPR and glucose to test treatment efficacy.

#### *Electrographic dysfunction*

Electrographic disturbances after ABI include non-convulsive seizures, pseudo-periodic discharges, as well as cortical spreading depolarisations (CSD), which may amplify cerebral damage. Using surface EEG and advanced monitoring with CMD and intracortical electroencephalography, researchers have been found seizures to be associated with increased LPR [11], the exact mechanisms of which are not entirely established. Of note, recent clinical CMD studies demonstrate that CSD cause significant alterations in neurochemistry (increase lactate, LPR and glutamate) in the absence of ischemia or anaerobic metabolism [12]. In this setting, CMD may be used to test the efficacy of future interventions targeted to seizure and CSD suppression.

## Microdialysis in research

With the use of large membrane cut-off catheters (100 vs. 20 kDa for standard catheters), CMD allows the measurement of large peptides/proteins for clinical research purposes.

### Neurodegeneration

Local brain measurement of tau (a biomarker of injury to thin non-myelinated axons; molecular weight ranging from < 20 to ~ 40 kDa) and neurofilament light-chain (NfL, a biomarker of injury to large-calibre myelinated axons; molecular weight 68 kDa) is possible using a 100-kDa CMD catheter. CMD—in combination to advanced brain MRI imaging—may be important to better characterize human brain pathology (e.g. traumatic axonal injury) [13] and help in designing future tailored interventions in specific patient subgroups.

### Blood–brain barrier functioning

Regional monitoring of neuroinflammation (e.g. cytokines, chemokines) and drug penetration across the blood–brain barrier (BBB) after ABI is nowadays possible with CMD [14]. Measuring the concentrations of drug molecules in the brain extracellular fluid is superior to cerebrospinal fluid or plasma to test the ability to effectively deliver pharmacological agents across the BBB into the brain, and is an important step in the development of central nervous system therapies. CMD provides pharmacokinetic information of variations with time in drug concentrations of brain interstitial tissue versus plasma and may help in testing the response of novel drugs on the cerebral extracellular milieu, or to assess drug penetration of pharmacologic agents [14].

## Implementation in the intensive care unit

Consensus guidelines for the use of CMD in acute brain pathologies help to guide CMD implementation. Although it is not currently employed at the same level as other monitors, particularly ICP, it is being increasingly applied (75 centres, personal communication: M-Dialysis AB Sweden). Addressing costs, human resources, and the complexity of the technique will increase the availability and performance of the technique [15], thereby facilitating its broader utilization in the future.

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**Compliance with ethical standards**

**Conflicts of interest**

The authors declare that they have no conflicts of interest.

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