# Microdialysis-based classifications of abnormal metabolic states following traumatic brain injury: a systematic review of the literature

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<th>Journal:</th>
<th>Journal of Neurotrauma</th>
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<td>Manuscript ID</td>
<td>NEU-2021-0502.R2</td>
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<tr>
<td>Manuscript Type:</td>
<td>Reviews</td>
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<tr>
<td>Date Submitted by the Author:</td>
<td>18-Aug-2022</td>
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</tbody>
</table>
| Complete List of Authors: | Venturini, Sara; Cambridge University, Department of Clinical Neurosciences   
 |  | Bhatti, Faheem; Cambridge University, Division of Neurosurgery, Department of Clinical Neurosciences   
 |  | Timofeev, Ivan; Cambridge University, Division of Neurosurgery, Department of Clinical Neurosciences   
 |  | Carpenter, Keri; Cambridge University, Division of Neurosurgery, Department of Clinical Neurosciences   
 |  | Hutchinson, Peter; Cambridge University, Division of Neurosurgery, Department of Clinical Neurosciences   
 |  | Guilfoyle, Mathew; Cambridge University, Division of Neurosurgery, Department of Clinical Neurosciences   
 |  | Helmy, Adel; Cambridge University, Division of Neurosurgery, Department of Clinical Neurosciences   |
| Keywords:        | MICRODIALYSIS, TRAUMATIC BRAIN INJURY, METABOLISM, ADULT BRAIN INJURY, MITOCHONDRIA |
| Manuscript Keywords (Search Terms): | cerebral microdialysis, multi-modality monitoring, lactate / pyruvate ratio, traumatic brain injury, mitochondrial dysfunction |
Dear Reviewers,

Thank you for taking the time to read and review our systematic review and provide feedback to improve our manuscript. We have addressed the comments raised regarding editing the language to improve readability. The revised version of the manuscript we are submitting incorporates these changes and we hope that you find this satisfactory.

Kind regards,
Sara Venturini (corresponding author)

Sara Venturini, BSc, MBChB, MPH
Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge, Cambridge CB2 0QQ, United Kingdom
Sv465@cam.ac.uk

Reviewer: 1

Comments to the Author
The authors have satisfyingly addressed the reviewers’ comments and the usability of the paper for the readership has improved. Some language editing may still be useful.

The manuscript has undergone further language editing to improve its readability.

Reviewer: 2

Comments to the Author
The authors have addressed the reviewers comments satisfactory.

No action required.
Microdialysis-based classifications of abnormal metabolic states following traumatic brain injury: a systematic review of the literature

Sara Venturini, Faheem Bhatti, Ivan Timofeev, Keri L.H. Carpenter, Peter J. Hutchinson, Mathew R. Guilfoyle, Adel Helmy

Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge; Cambridge, UK

Corresponding author:
Miss Sara Venturini, BSc, MBChB
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
sv465@cam.ac.uk
tel: +44 7557387802 / +44 1223 336946

Faheem Bhatti
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
Fib21@cam.ac.uk
tel: +44 1223 336946

Ivan Timofeev
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
Ivan.timofeev@addenbrookes.nhs.uk
Tel: +44 1223 336946

Keri L.H. Carpenter, PhD
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
Klc1000@cam.ac.uk
Tel: +44 1223 336946

Peter J. Hutchinson
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
Pjah2@cam.ac.uk
Tel: +44 1223 336946

Mathew Guilfoyle
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
Mathew.guilfoyle@addenbrookes.nhs.uk
Tel: +44 1223 336946
Adel Helmy
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
adelhelmy@cantab.net
Tel: +44 1223 336946

Keywords: cerebral microdialysis, multi-modality monitoring, lactate / pyruvate ratio, traumatic brain injury, mitochondrial dysfunction
Abstract
Following traumatic brain injury (TBI), cerebral metabolism can become deranged, contributing to secondary injury. Cerebral microdialysis (CMD) allows cerebral metabolism assessment and is often used with other neuro-monitoring modalities. CMD-derived parameters such as the lactate/pyruvate ratio (LPR) show a failure of oxidative energy generation. CMD-based abnormal metabolic states can be described following TBI, informing the aetiology of physiological derangements. This systematic review summarizes the published literature on microdialysis-based abnormal metabolic classifications following TBI.

Original research studies where the populations were patients with traumatic brain injury were included. Studies that described CMD-based classifications of metabolic abnormalities were included in the synthesis of the narrative results synthesis. A total of 825 studies underwent two-step screening after duplicates were removed. Fifty-three articles that used CMD in TBI patients were included. Of these, 14 described abnormal metabolic states based on CMD parameters. Classifications were heterogeneous between studies. LPR was the most frequently used parameter in the classifications; high LPR values were described as metabolic crisis. Ischaemia was consistently defined as high LPR with low CMD substrate levels (glucose or pyruvate). Mitochondrial dysfunction, describing inability to use energy substrate despite availability, was identified based on raised LPR with near-normal levels of pyruvate.

This is the first systematic review summarizing the published literature on microdialysis-based abnormal metabolic states following TBI. Although variability exists between individual classifications, there is broad agreement around broad definitions of metabolic crisis, ischaemia and mitochondrial dysfunction. Identifying the aetiology of deranged cerebral metabolism after TBI is important to offer targeted therapeutic interventions.
Introduction

Cerebral microdialysis (CMD) was first described in 1974 and started to be used clinically in the 1990s. Since then, CMD has evolved to become one of the established modalities to invasively monitor traumatic brain injury patients. CMD involves sampling brain parenchymal extracellular fluid through a microdialysis catheter which possesses a semipermeable membrane (as its outer wall). This, which is inserted in the brain parenchyma and allows diffusion of water and solutes between the perfusate (flowing through the microdialysis catheter at a constant rate) and surrounding brain extracellular fluid. Collection and analysis of CMD samples, also termed microdialysate, provides information on brain chemistry states and brain metabolism.

CMD analytes are varied and include metabolic parameters such as glucose, lactate, pyruvate, glutamate, glycerol, as well as cytokines and other molecules used as biomarkers. The predominant clinical application of CMD has been in the assessment of brain metabolism, particularly following traumatic brain injury (TBI). CMD data is usually collected as part of multi-modality neuromonitoring together with intracranial pressure (ICP) and brain tissue oxygen tension (PbtO2).

The most widely investigated CMD-derived parameter reflecting deranged cellular metabolism is lactate/pyruvate ratio (LPR). The LPR has emerged as a marker of redox state, with high LPR values above 25 correlating with poor outcome, and therefore designated as pathological and indicating a shift towards “anaerobic” metabolism. It is important to note that the LPR cut-off of 25 is a statistical association rather than an absolute marker for poor outcome, and some degree of overlap exists between outcome groups showing LPR>25. Nevertheless, similar relationships have been described across several studies with LPR>25 remaining a robust biomarker. The pathophysiological processes that lead to a rise in LPR are varied, with evidence that LPR can be raised in cerebral hypoxia or ischaemia, i.e. lack of oxygen delivery of oxygen (hypoxia), or lack of both oxygen and energy substrates (ischaemia). LPR can also be raised, but also by due to shortage of available energy substrate, due to over-consumption, such as hyper-glycolysis, or disrupted cellular metabolism due to mitochondrial dysfunction. Additionally, the relationship between deranged LPR and other multimodal monitoring parameters such as pyruvate, glucose, ICP, CPP, PbtO2 differs between studies.

Using information from CMD together with ICP and PbtO2, abnormal metabolic states following TBI have been described using information from CMD together with ICP and PbtO2. These may define specific subsets of patients with
defined specific metabolic derangements that may benefit from targeted therapeutic strategies. However, to this date, there has been no detailed systematic review of the literature evaluating the abnormal metabolic states following TBI, described using CMD data.

This study aims to systematically review the published literature on the different abnormal metabolic states following TBI which have been categorized using cerebral microdialysis-derived parameter combinations of parameters, and. It also aims to describe their evolution over time.

Specifically, this review addresses the following questions:

- Do studies using cerebral microdialysis allow classification of abnormal metabolic states after TBI based on CMD data?
- What are the abnormal metabolic states following TBI, classified using cerebral microdialysis?
- Have the cerebral microdialysis-driven classifications of abnormal metabolic states following TBI changed over time?
- How do different classifications used to describe impaired cerebral metabolism following TBI overlap?

Materials and Methods

This systematic review was conducted using the methods outline in the Cochrane Handbook for Systematic Reviews. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Protocol and registration

The protocol for this review was published on PROSPERO, an international prospective register of systematic reviews, on 27/01/2021 (PROSPERO registration number: CRD42021232365).

Eligibility criteria

The inclusion and exclusion criteria used in this review are presented in full in Table 1.
Population and injury model

Human studies in which patients had suffered traumatic brain injury, severe enough to require intubation, ventilation and invasive neuromonitoring, were the focus of this review. Studies involving animal models or non-traumatic brain injury were excluded.

Intervention and Outcomes

Studies were included if cerebral microdialysis was used to monitor cerebral metabolic parameters such as lactate, pyruvate, lactate/pyruvate ratio, glucose, glutamate and glycerol. Studies that did not utilize cerebral microdialysis were excluded. Similarly, studies which utilized microdialysis to measure non-metabolic parameters e.g. cytokine concentrations, drug concentrations or tau protein concentrations were excluded. Studies were not excluded based on the duration or frequency of cerebral microdialysis.

Information sources

To identify articles, a systematic search was performed on the MEDLINE and Embase databases on April 20th 2022.

Search

The terms used to search MEDLINE and Embase are described in Table 2. The final search was performed using the Ovid platform, utilizing the tool allowing searching multiple databases simultaneously. Articles in English were selected, no additional search limits were applied.

Study selection

Duplicates of the studies were identified and removed in Ovid using the in-built deduplication function. Following removal of duplicates, each of the titles and abstracts was screened independently by two of the authors (SV, FB) using the Rayyan software package. Full-text review of the selected studies was subsequently performed independently by two reviewers (SV, FB) before combining the two ratings. Disagreements were resolved through discussion between the reviewers until mutual agreement was reached.

Data Extraction and Synthesis
Data were extracted using a custom-made data extraction sheet. Data points extracted were author, year of publication, country and center in which the study was conducted, study characteristics (e.g. study design), sample characteristics (e.g. population size, age, GCS range of participants, TBI severity), intervention (e.g. location of microdialysis probe), the metabolic parameters measured, the cut-off values used to define normal and abnormal values for the different metabolic parameters (such as the LPR), and the nature of any neurometabolic groups which were identified.

Data extraction for all the included studies was performed by one author (SV). A subset of 10 studies (20% of the total) were randomly selected (using a random-number generator in R) to undergo data extraction by a second author (FB), to confirm inter-rater reliability agreement of the extracted data points. The agreement between the two independent data extraction processes was excellent with no conflicts.

No quantitative analysis (meta-analysis) was performed, because the aim of this review was to assess classification systems.

Quality of the evidence and risk of bias
Risk of bias and methodological quality were assessed with a custom-made quality assessment tool based on the Critical Appraisal Skills Programme (CASP) checklists for observational studies, to include items specific to the research question. The full custom-made checklist is available in Appendix 1 (Supplemental material). This risk of bias assessment was applied to the studies describing abnormal metabolic states included in the full analysis. Overall, quality ratings were assigned to each study as follows:

- “N” ratings in any domain, or more than two “unclear” ratings → poor quality
- Maximum of two “unclear” ratings → fair quality
- Maximum of one “unclear” rating → good quality.

The Grading of Recommendation Assessment Development and Education (GRADE) criteria were used to assess the level of evidence for the metabolic state classifications identified. The GRADE classification is split into four levels: high - representing high evidence with multiple high-quality studies with consistent results, moderate - representing moderate evidence with one high-quality study or multiple low-quality studies, low - representing low
evidence with one or more studies with severe limitations, and very low - representing very low evidence based on expert opinion or few studies with severe limitations.

Results

Search results and study selection

The search strategy produced a total of 825 individual studies, after duplicates were removed. After initial screening of titles and abstracts, 199 studies underwent full-text review. Of these, 53 records were included in this review. The PRISMA Flow diagram summarizing this is presented in figure 1, including reasons for exclusion of all articles read in full text.

Study characteristics

All 53 studies were observational studies, with the majority (45/52) being performed in a prospective fashion. Summary details of all 53 studies are included in Appendix 2 (Supplemental Material). These 53 studies were conducted across 11 countries and 21 individual institutions. The population size varied widely across studies, from 5 to 619. In total, this comprised 3211 TBI patients across the studies. All studies state they included patients with moderate-severe TBI, identified as either a GCS of less than 8, or a higher GCS with imaging finding consistent with severe brain injury, such as diffuse axonal injury, mass effect with midline shift, large intracranial haematomas, or cerebral oedema.

Identifying abnormal metabolic states: synthesis of the results

Fourteen studies described abnormal metabolic states based on inclusion of cerebral microdialysis parameters. These studies were therefore included in the next steps of the data synthesis steps. Together, these studies had a total population of 1582 TBI patients.

CMD probe location, sampling technique and timing of monitoring

Most of the studies described the location used for the CMD probe in their subjects (51/53). The most common location used for the CMD probe was the right frontal lobe, used in 35 studies, aiming for macroscopically normal brain. Thirteen studies placed the CMD probe in...
the penumbra of a focal lesion (perilesional). Three studies had two CMD probes inserted in all subjects, one in the penumbra of a focal lesion and one in healthy-looking brain. When looking specifically at the 14 studies describing abnormal metabolic states, variation in probe location remained: 8 specified a right frontal location in macroscopically normal brain location; 3 were perilesional; one was ipsilateral to the injured hemisphere; and two had unspecified parenchymal locations.

All but one study (with one exception (Bullock et al. [REF])\textsuperscript{21}, the studies that we reviewed described hourly sampling of microdialysate, offering conferring a degree of standardisation across study sampling techniques. CMD sampling frequency is relevant because longer sampling periods would potentially result in less granular data\textsuperscript{21}. Studies primarily monitored patients for the first few days following TBI, with many starting from the day of the injury itself. Five studies specifically reported that monitoring started on day 0 from injury\textsuperscript{21,27,39,51,66}. The minimum reported monitoring period of monitoring was at least 12 hours\textsuperscript{50}, with several studies reporting a monitoring duration in the range of 3-5 days from injury range. Only one study\textsuperscript{2} by Svedung Wettervik et al.\textsuperscript{2} stipulated a longer 10-day monitoring period [REF].

Classifications of abnormal metabolic states

Detailed parameters used in the classifications included in the 14 studies are summarised in Table 3. As detailed described further later in this section, marked differences regarding terminology and definitions of metabolic states existed between across various studies, as described later in this section.

Most studies used CMD parameters alone to define abnormal metabolic categories; figure 2 below summarises how the classification systems in different papers overlap with each other. Some studies used additional parameters from other modalities in combination with CMD metrics. For example, Hlatky et al. combined PbtO\textsubscript{2} readings with CMD to identify hypoperfusion\textsuperscript{30}. Marini et al. described metabolic states as well as cerebral blood flow abnormality states based on CPP and cerebral oxygen extraction measured through near infrared spectroscopy. Severe metabolic crisis was associated with type 2 flow abnormality (CPP >60 mmHg with PbtO\textsubscript{2} <20 mmHg), likely due to ischaemia as the underlying pathology.
Sala et al. investigated cerebral lactate metabolism using CMD and PbtO2 monitoring51. Most raised lactate episodes of raised lactate concentration were associated with glycolysis and normal PbtO2, rather than with hypoxia. Perfusion CT scans were also obtained. Glycolytic lactate was associated with normal or supranormal brain perfusion, whereas hypoxic lactate was associated with globally reduced brain perfusion of brain.

Svedung Wettervick et al. investigated the relationship between arterial oxygenation (pO2) and cerebral metabolism following TBI62. Pattern A ("energy metabolic disturbances, limited substrate supply") was associated with lower pO2 values (p<0.001). Higher mean arterial pO2 was associated with lower CMD lactate levels, and in cases of limited pyruvate supply, arterial pO2 was higher where oxidative metabolism was preserved (normal LPR).

Vespa et al. combined CMD metabolites data with PET imaging to study the cause of metabolic crisis66. Metabolic crisis was defined by an LPR >40, whereas ischaemia was described as LPR >40 with cerebral glucose <0.2 mmol/L, or as an oxygen extraction fraction (OEF) >0.75 using PET criteria. Metabolic crisis occurred in 25% of monitoring, but ischaemia only occurred in 2.4% using CMD parameters and in 1% using PET criteria. Combining this with PET parameters, LPR correlated negatively with the cerebral metabolic rate of oxygen (CMRO2).

Nordstrom et al. noted that the mitochondrial dysfunction pattern was more common than the ischaemic pattern45. They also studied biochemical patterns in relation to TBI lesions. Patients with extradural haematoma and no mass lesion were more likely to have normal LPR, whereas patients with subdural haematoma or haemorrhagic contusions had higher LPR values45.

Relation to outcomes

Twenty-seven studies described how monitoring parameters relate to outcome. A range of clinical outcome measures were addressed. These included mortality (8 studies), favourable or unfavourable outcome described by the Glasgow Outcome Score (GOS) (13 studies), presence of spreading depolarisation (1 study), and development of frontal lobe atrophy (1 study).

Of the 14 studies classifying abnormal metabolic states, 7 assessed correlations with outcome. Bullock et al. and Chamoun et al. showed that raised glutamate was associated with poor functional neurological outcome and increased mortality21,22. Eiden et al. identified a ‘healthier’ metabolic pattern characterized by higher levels of CMD lactate,
pyruvate and glucose, and lower levels of glutamate and ICP, a pattern which was associated with better functional outcomes (Glasgow Outcome Scale Extended) at 6 months\textsuperscript{25}.

Gupta et al. studied CMD parameters in patients with severe TBI who had undergone decompressive craniectomy\textsuperscript{27}. Patients with poor outcomes (measured as GOS at 6 months) had higher proportion of both mitochondrial dysfunction (LPR >25 and pyruvate >70 μmol/L) and ischaemia\textsuperscript{25} (LPR >25 and pyruvate <70 μmol/L) (p<0.001) compared to those with favourable outcome.

Marini et al. also found an association between metabolic crisis and higher likelihood of being a non-survivor\textsuperscript{39}.

Stein et al. showed that metabolic crisis (LPR >25 and glucose <0.8 mmol/L) was common, seen in (74\%) of their patients, despite normal ICP\textsuperscript{54}. Moreover, patients with unfavourable outcome (GOS-E \leq 6 at 6 months) spent longer in the state of metabolic crisis state (p = 0.011)\textsuperscript{54}.

Timofeev et al. addressed how cerebral hypoxia and acidosis relate to mortality in TBI and how these relate to disturbances of cerebral metabolism\textsuperscript{57}. Four states were described based on PbtO2 and cerebral extracellular pH (pHbt). State 1 showed with low PbtO2 and low pHbt, state 2 had normal PbtO2 and low pHbt, state 3 was characterized by low PbtO2 and normal pHbt, and state 4 with normal PbtO2 and normal pHbt. State 2 was associated with the highest levels of LPR, lactate and glucose, whereas state 1 showed high LPR with reduced glucose (p<0.001). State 2 was also associated with the highest mortality (p=0.021).

Guilfoyle et al. found that raised LPR in days 3 – 7 after injury was more likely in the poor outcome group, and that high LPR was an independent predictor of ordinal clinical outcome 7 months post-injury, dichotomized into favourable (Glasgow Outcome Scale 4-5) and unfavourable (GOS 1-3)\textsuperscript{65}. Moreover, the relationships between LPR and CPP< PbtO2 and brain glucose directly suggest therapeutic goals that could be adopted to improve cerebral metabolism.

Analysis of Risk of bias analysis
Risk of bias assessment was performed for the studies that described abnormal metabolic states, as these were included in the amalgamation of the evidence synthesis. A custom-made
risk of bias assessment (Appendix 1) was used, and the results are summarized in Table 4 below.

Methodological quality was overall good across the studies, with the majority describing clear methodology. The main area prone to bias that affected all studies was the lack of clear description if confounding factors and measures taken to account for these. Additionally, in a number of studies, a detailed description of how the subjects were recruited could have been strengthened, specifically with regards to whether all consecutive eligible patients were included or whether another method to obtain the patient sample was used (e.g. random sample). Follow-up is important to the results; follow-up, which was reported as complete (greater than 85%) in all 14 studies. This is especially relevant to evaluation of outcome, as incomplete follow-up may result in introduction of bias.

GRADE: level of evidence

GRADE ratings were used to evaluate the quality of evidence for each of the main metabolic abnormalities described across the included studies, namely: metabolic crisis, ischemia, mitochondrial dysfunction. These are summarized as follow in Table 5.

Discussion

Of the 53 studies identified in this review as using CMD monitoring in TBI patients, only 15% (14 studies) described classifications of abnormal metabolic states based on CMD parameters, sometimes in conjunction with other monitoring modalities.

Are the classifications describing the same phenomena?

To evaluate if there is significant overlap across the classifications described in the studies included in this review, it is important to consider how energy generation occurs in the brain. Glucose is the preferred energy substrate for neurons through the process of glycolysis, however, although neurons can also utilize lactate as a substrate through the astrocyte-neuron lactate shuttle (ANLS). In aerobic conditions, for every molecule of glucose metabolized via the three-stage pathway of glycolysis, TCA cycle and electron transport chain, the theoretical maximum overall yield is 36-38 molecules of ATP, but the actual yield is considered somewhat lower. Under anaerobic conditions, or in cases of mitochondrial dysfunction, pyruvate is converted to lactate by the enzyme lactate dehydrogenase (LDH) in the cytosol, instead of entering the
mitochondrial TCA cycle. This shift increases the ratio between lactate and pyruvate (LPR or lactate/pyruvate ratio), which is therefore a measure of the metabolic redox state.

The above processes are summarized in figure 3, reproduced from Carpenter et al.67.

Pathological conditions relevant to patients with TBI, including cerebral ischaemia that can arise in the context of raised intracranial pressure, altered cerebral autoregulation, or insufficient oxygen supply affect these metabolic processes. Inadequate energy substrate supply such as scarcity of glucose can also contribute to abnormalities, and finally impaired utilization of the available energy substrates due to cellular damage can also occur.

The role of CMD probe location and monitoring timing

Cerebral microdialysis allows assessment of focal rather than global metabolism, making probe location an important factor in result interpretation. For example, Timofeev et al. studied microdialysis catheter location, showing that decreases in perfusion and oxygenation were associated with deteriorating neurochemistry, and these effects were more pronounced in perilesional tissue and when cerebrovascular reactivity was impaired70.

Probe locations varied widely, and in a minority of studies multiple rather than single probes were used. Due to small numbers and heterogeneity, stratification for probe location was not possible for systematic comparison of metabolic states. In future work, separation between probes located in peri-lesional tissue versus “normal” brain should be adopted.

Timing and duration of monitoring is also relevant, on account of the dynamic nature of the pathophysiological processes occurring in the acute phase following TBI. Most studies included in this review monitored patients for the first 3-5 days following injury. In future work, it would be relevant to standardize monitoring protocols to assess different phases of metabolic abnormality following initial injury and facilitate comparison across studies. For example, Guilfoyle et al. found a rising trend in LPR from 48 hours after TBI for up to two weeks, in patients undergoing prolonged monitoring.65. Further investigation of whether different metabolic patterns occur at pre-determined time points following injury, for example 24, 48, 72, 96 hours, would provide additional information on evolving abnormal metabolic processes.

Metabolic crisis
Several studies define the abnormal cerebral metabolic state of metabolic crisis. Metabolic crisis is one of the commonly defined abnormal metabolic states in the studies included in this review\textsuperscript{39,54,66}. Metabolic crisis is used as a description of a state where the LPR is raised above normal values (>25, although higher cut-offs such as 40 have also been used). Metabolic crisis appears to be an umbrella descriptor, primarily defined by high LPR alone, and allowing for sub-categories depending on the cause of metabolic crisis identified, such as ischaemia/ischemia or mitochondrial dysfunction.

Classifications of ischaemia

Ischaemia/ischemia is often described by the papers included in this review as an abnormal metabolic state. Based on CMD parameters, ischaemia/ischemia definitions often include raised LPR values above 25 together with markers of “anaerobic” metabolism, such as low glucose levels\textsuperscript{30,66}, low pyruvate levels\textsuperscript{27,39,45}, or high lactate\textsuperscript{50,51}. Vespa et al. in 2005 discussed the incidence of ischaemia/ischemia post TBI is low both in terms of regional ischaemia/ischemia (CMD) and global ischaemia/ischemia (PET)\textsuperscript{66}. Although overt ischaemia/ischemia is uncommon with modern neurocritical care, microvascular ischaemia/ischemia has been evidenced by advanced imaging in some situations\textsuperscript{71,72}. The majority of metabolic crisis is non-ischaemia/ischemic and as such LPR is a non-specific indicator of ischaemia/ischemia as it simply reflects an impaired redox state which may result from other mechanisms such as mitochondrial dysfunction.

Classifications of mitochondrial dysfunction

Mitochondrial dysfunction can be described as an abnormal metabolic state where there is impairment of the cell’s ability to utilise energy substrate such as glucose or pyruvate and oxygen, despite adequate supply. There is some variation in the exact cut off used for normal values among the studies, but all the definitions of mitochondrial dysfunction identified use a raised LPR and a normal level of pyruvate\textsuperscript{27,39,45}. This is in keeping with a problem further downstream to the lack of energy substrate. This definition overlaps or coincides with Pattern C identified by Svedung Wettervik et al., described as abnormal metabolism with adequate pyruvate supply\textsuperscript{62}.

The role of energy substrates

Glucose was used in several classifications. Importantly, low CMD glucose is a feature of abnormal metabolic states, rather than high glucose. This reflects the primacy of glucose for
neuronal energy generation in aerobic conditions. Furthermore, the goal directed avoidance of hyperglycaemia in intensive care protocols avoids very high levels of systemic glucose which may be translate into raised CMD glucose.

Low glucose combined with high LPR was classified as ischaemia by Vespa. Eiden noted that glucose was overall higher in the healthier metabolic pattern A, perhaps indicating preserved substrate supply. This is in line with the latest cerebral microdialysis consensus statements, where low brain glucose together with high LPR is suggested to signify ischaemia and/or tissue hypoxia. High CMD glucose has also been associated with unfavourable outcome, as described in the same consensus statement. This seems to suggest that an optimal range for brain glucose exists, and deviation from this in either direction is undesirable in TBI. In healthy states, serum glucose concentration and control influence brain glucose, but evidence suggests this relationship may be lost in brain injury. For example, other secondary pathological phenomena occurring after TBI such as spreading depolarization may cause rapid reduction in brain glucose.

There is variation in the levels that have been described as normal for pyruvate, some studies using values around 70 µmol/L and other studies using higher cut off values around 120 µmol/L. There is no robust consensus on the threshold for normal pyruvate with wide ranges reported in the literature, adding to the heterogeneity in cut offs used. Further work to determine the best threshold would provide evidence to complement our understanding of normal values found within the brain. Additionally, as CMD is an invasive monitoring technique, there is little available data from normal human brain of individuals without brain injury. Authors often use non-lesion TBI brain for this, however this ignores the fact that there can be diffuse, widespread injury. Previous work by our group using 31P MRS described that biochemical abnormalities exist in the absence of radiologically-visible injury based on conventional and advanced MRI. The few studies that included normal (non-TBI) brain performed CMD in normal-appearing brain tissue in patients undergoing surgery for benign tumours. Despite this variation, there is agreement across the studies that the combination of high LPR and low pyruvate levels describe states of ischaemia, whereas high LPR with normal or near normal pyruvate are in line with mitochondrial dysfunction or states with preserved substrate supply but impairment in substrate utilisation.
The role of lactate in cerebral metabolism is yet to be fully understood, with evidence that it increases in states of injury and anaerobic metabolism, but it can also be a useful energy fuel for example through the ANLS\textsuperscript{34}. Using microdialysis delivery of 3-\textsuperscript{13}C lactate in TBI patients, Gallagher et al. and Jalloh et al. showed that lactate was metabolised via the TCA cycle\textsuperscript{34,81}. Sahuquillo et al. used lactate in conjunction with LPR and identified two metabolic states with raised lactate >2.5 mM. High lactate and high LPR indicates anaerobic metabolism, whereas high lactate and normal LPR suggests aerobic hyperglycolysis\textsuperscript{50}. Similarly, Sala et al. described a hypoxic lactate state characterised by high lactate and low brain tissue oxygen tension, and a glycolytic lactate state, where lactate is raised but with normal oxygenation and normal pyruvate levels\textsuperscript{61}. Finally, it should be remembered that pyruvate and lactate are not just produced by glycolysis. Pyruvate can also be a spin-out product of the TCA cycle (termed cataplerosis) and then either recycled (via acetate) back into the TCA cycle, or converted by lactate dehydrogenase into lactate that can exit the cell\textsuperscript{82}.

Glutamate-based classifications

Two papers used glutamate levels to determine metabolic states\textsuperscript{21,22}, indicating that higher or rising glutamate levels are associated with worse clinical outcomes, however this phenomenon was noted in isolation and not related to other CMD parameters. Raised glutamate may reflect a reduced capacity for astrocytic uptake at times of metabolic stress. Although these classification algorithms incorporate glutamate thresholds, this may reflect the putative role of glutamate in excitotoxicity-induced injury, rather than a presumption that glutamate plays a role in energy generation directly.

No other papers focused on glutamate as a parameter to focus on for further classification, perhaps reflecting evidence from the latest cerebral microdialysis consensus meeting stating that other parameters (such as LPR, glucose) are more useful than glutamate in offering information on deranged metabolism\textsuperscript{73}. In a CMD study of 619 TBI patients, glutamate levels were generally higher in the unfavourable outcome group (vs. favourable outcome group), but not significantly different\textsuperscript{65}. Glutamate therefore does not appear to be a strong candidate for thresholding in classification algorithms.

The wider context

The results of this review were interpreted in the context of the latest cerebral microdialysis consensus statement published in 2015\textsuperscript{73}. From a methodological perspective, most papers...
adhered to the recommendations to describe the location of the CMD probe and data acquisition techniques. Abnormal threshold values exhibit some variation, but overall fall within the ranges described by the consensus statement.

In a review published in 2017, our group describes a stepwise approach to assess the aetiology of raised LPR in TBI patients, summarised in Table 6. The monitoring parameters used (ICP, PRx, brain tissue oxygen, brain glucose concentration and LPR) help guide therapy and correct physiological abnormalities in a stepwise fashion.

Although multiple neurometabolic abnormalities can co-exist, it is important to identify the cases of mitochondrial dysfunction that are present despite implementation of standard neuro-intensive care intervention, as these instances are where novel therapeutic modalities are needed due to the lack of standard treatment.

More recently, the same algorithm was used to identify TBI patients showing the mitochondrial dysfunction pattern. In this group of patients, disodium 2,3-13C2 succinate was administered focally through the microdialysis catheter to five patients and resulted in a reduction in LPR, suggesting that exogenous succinate may represent a targeted intervention to treat mitochondrial dysfunction. Also, the 13C-labelling patterns in the metabolites indicated that TCA cycle metabolism of the 2,3-13C2 succinate occurred.

Limitations
The studies included were heterogeneous with regards to various methodological aspects of their methodology. Their standard procedures for multimodality monitoring varied; notably, CMD probes had heterogeneous locations. Although the majority were placed in the standard location of the right frontal lobe (often adjacent to ICP / PbtO2 monitors), some had other locations such as in the penumbra of a focal lesion, or ipsilateral to a mass lesion. As microdialysis samples local metabolism, probe location near to or away from a mass lesion could affect the values of CMD parameters sampled.

Additionally, heterogeneity was present in the parameters used for classifications of abnormal brain metabolism, limiting the strength of the evidence for each individual parameter.

A second limitation was in the small population sizes in some of the included studies, with numbers ranging from as low as 19 to as many as 619. It is possible that some of the studies with small populations are under-powered, limiting the strength of their conclusions.
All the studies included were observational in nature. Although observational studies can be perceived as having lower quality of evidence compared to randomized studies, they are powerful in describing the incidence or prevalence of pathophysiological states and are therefore appropriate for the research question of this review.

**Future steps towards standardization**

This review identifies steps that could be taken in future studies to achieve better standardization and more robust classification of abnormal metabolic states. Firstly, defining key time points to assess metabolic abnormalities would be important, to better evaluate and compare temporal changes occurring following injury. Secondly, agreement on threshold values for each parameter of interest is advised, to limit the heterogeneity seen in included studies (for example, cut-offs for abnormal pyruvate levels varied). Thirdly, clear description for CMD probe location in relation to the TBI present is important. Finally, adopting uniform outcome assessments would facilitate result pooling and correlation of abnormal metabolic states to clinical outcomes. Future prospective studies incorporating the above suggestions would facilitate strengthening of the evidence, with the aim to standardize abnormal metabolic states and plan targeted interventions that are reproducible, so that their impacts can be measured.

**Overall, the results summarise suggest** that abnormal metabolism, defined as metabolic crisis, ischaemia or mitochondrial dysfunction appears to be associated with worse outcome. Therefore, therapeutic goals that could be adopted to improve cerebral metabolism should be a research focus.

**Conclusions**

This systematic review aimed to summarize the published literature on microdialysis-derived abnormalities of metabolic states following TBI. Of these studies describing cerebral microdialysis monitoring in TBI, a small number formally attempted to classify abnormal metabolic states identified in their patient populations. This review confirmed that LPR >25 is consistently described as a reliable marker for abnormal cerebral metabolism, and that such elevated LPR can have several aetiologies.

The term “metabolic crisis” appears to be used to describe states of abnormal metabolism with raised LPR, but it is broad and can encompass ischaemic.
metabolism, or substrate depletion, or mitochondrial dysfunction, depending on the classifications used. Combining LPR with other variables can be classified as categorizing the abnormal states of ischaemia and mitochondrial dysfunction.

This review also identified the fact that there is still lack of complete agreement on what parameters and cut-off values are best for the identification of different abnormal metabolic states. It also showed that combining CMD data with other monitoring modalities can offer more information on the aetiologies of abnormal brain metabolism in the context of TBI.

Finally, since the metrics of several classification algorithms overlap in the metrics they utilise, a comparative study of the various methods can help to identify areas of overlap.

The great advantage of LPR as a metric of energy failure is that it directly reflects the biochemical redox state within the brain. However, to target and direct appropriate therapies aimed at correcting such abnormalities, the underlying pathological state must be robustly identified, driving the need for accurate classification of metabolic abnormalities.
Authors’ Contributions

S.V. and A.H. designed the study protocol. S.V. and F.B. performed the screening, data extraction and manuscript writing processes. A.H., M.G., P.J.A.H. and K.L.H.C. critically revised the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

P.J.A.H. is a director of Technicam (Newton Abbot, UK), the manufacturer of the cranial access device used in several of the microdialysis studies cited in this article. The other authors have no conflict of interests to declare.

Funding acknowledgments

The authors disclose receipt of the following financial support for the research, authorship, and/or publication of this article: Medical Research Council (Grant no. G1002277 ID98489) and National Institute for Health and Care Research Biomedical Research Centre, Cambridge (Neuroscience Theme; Brain Injury and Repair Theme). Authors’ support; PJH–National Institute for Health Research and Care (Professorship, Biomedical Research Centre, Brain Injury MedTech Co-operative, Senior Investigator Award and the Royal College of Surgeons of England; KLHC–National Institute for Health and Care Research Biomedical Research Centre, Cambridge (Neuroscience Theme; Brain Injury and Repair Theme); AH–Medical Research Council/Royal College of Surgeons of England Clinical Research Training Fellowship (Grant no.G0802251), the NIHR Biomedical Research Centre and the NIHR Brain Injury MedTech Co-operative; SV-NIHR Academic Clinical Fellowship in Neurosurgery. The views expressed are those of the Authors and are not necessarily those of the NIHR or of the Department of Health and Social Care or of any of the other funding bodies.
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Microdialysis-based classifications of abnormal metabolic states following traumatic brain injury: a systematic review of the literature

Sara Venturini, Faheem Bhatti, Ivan Timofeev, Keri L.H. Carpenter, Peter J. Hutchinson, Mathew R. Guilfoyle, Adel Helmy

Division of Neurosurgery, Department of Clinical Neurosciences, University of Cambridge; Cambridge, UK

Corresponding author:
Miss Sara Venturini, BSc, MBChB
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
sv465@cam.ac.uk
tel: +44 7557387802 / +44 1223 336946

Faheem Bhatti
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
Fib21@cam.ac.uk
Tel: +44 1223 336946

Ivan Timofeev
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
Adel Helmy
Division of Neurosurgery
Department of Clinical Neurosciences
University of Cambridge
Cambridge CB2 0QQ
United Kingdom
adelhelmy@cantab.net
Tel: +44 1223 336946

Keywords: cerebral microdialysis, multi-modality monitoring, lactate / pyruvate ratio, traumatic brain injury, mitochondrial dysfunction
Abstract

Following traumatic brain injury (TBI), cerebral metabolism can become deranged, contributing to secondary injury. Cerebral microdialysis (CMD) allows cerebral metabolism assessment and is often used with other neuro-monitoring modalities. CMD-derived parameters such as the lactate/pyruvate ratio (LPR) show a failure of oxidative energy generation. CMD-based abnormal metabolic states can be described following TBI, informing the etiology of physiological derangements. This systematic review summarizes the published literature on microdialysis-based abnormal metabolic classifications following TBI.

Original research studies where the populations were patients with traumatic brain injury were included. Studies that described CMD-based classifications of metabolic abnormalities were included in the synthesis of the narrative results.

A total of 825 studies underwent two-step screening after duplicates were removed. Fifty-three articles that used CMD in TBI patients were included. Of these, 14 described abnormal metabolic states based on CMD parameters. Classifications were heterogeneous between studies. LPR was the most frequently used parameter in the classifications; high LPR values were described as metabolic crisis. Ischemia was consistently defined as high LPR with low CMD substrate levels (glucose or pyruvate). Mitochondrial dysfunction, describing inability to use energy substrate despite availability, was identified based on raised LPR with near-normal levels of pyruvate.

This is the first systematic review summarizing the published literature on microdialysis-based abnormal metabolic states following TBI. Although variability exists between individual classifications, there is broad agreement around broad definitions of metabolic crisis, ischemia and mitochondrial dysfunction. Identifying the etiology of deranged cerebral metabolism after TBI is important for targeting therapeutic interventions.
Introduction

Cerebral microdialysis (CMD) was first described in 1974 and started to be used clinically in the 1990s\textsuperscript{1,2}. Since then, CMD has evolved to become one of the established modalities to invasively monitor traumatic brain injury patients. CMD involves sampling brain parenchymal extracellular fluid through a catheter which possesses a semipermeable membrane (as its outer wall). This is inserted in the brain parenchyma and allows diffusion of water and solutes between the perfusate (flowing through the microdialysis catheter at a constant rate) and surrounding brain extracellular fluid\textsuperscript{3}. Collection and analysis of CMD samples, also termed microdialysate, provides information on brain chemistry states and brain metabolism.

CMD analytes are varied and include metabolic parameters such as glucose, lactate, pyruvate, glutamate, glycerol, as well as cytokines and other molecules used as biomarkers\textsuperscript{4}. The main clinical application of CMD has been in the assessment of brain metabolism, particularly following traumatic brain injury (TBI)\textsuperscript{5}. CMD data is usually collected as part of multimodality neuromonitoring together with intracranial pressure (ICP) and brain tissue oxygen tension (PbtO\textsubscript{2})\textsuperscript{6}.

The most widely investigated CMD-derived parameter reflecting deranged cellular metabolism is lactate/pyruvate ratio (LPR)\textsuperscript{7}. The LPR has emerged as a marker of redox state, with high LPR values above 25 correlating with poor outcome, and therefore designated as pathological and indicating a shift towards “anaerobic” metabolism\textsuperscript{6}. It is important to note that the LPR cut-off of 25 is a statistical association rather than an absolute marker for poor outcome, and some degree of overlap exists between outcome groups showing LPR>25\textsuperscript{8}. Nevertheless, similar relationships have been described across several studies with LPR>25 remaining a robust biomarker. The pathophysiological processes that lead to a rise in LPR are varied, with evidence that LPR can be raised in cerebral hypoxia or ischemia, i.e. lack of oxygen delivery (hypoxia), or lack of both oxygen and energy substrates (ischemia). LPR can also be raised due to shortage of available energy substrate, due to over-consumption, such as hyper-glycolysis, or disrupted cellular metabolism due to mitochondrial dysfunction\textsuperscript{3}. Additionally, the relationship between deranged LPR and other multimodal monitoring parameters such as pyruvate, glucose, ICP, CPP, PbtO\textsubscript{2} differs between studies. Abnormal metabolic states following TBI have been described using information from CMD together with ICP and PbtO\textsubscript{2}. These may characterize subsets of patients with specific metabolic derangements that may benefit from targeted therapeutic strategies\textsuperscript{9}.
However, to date, there has been no detailed systematic review of the literature evaluating the abnormal metabolic states following TBI, described using CMD data.

This study aims to systematically review the published literature on the different abnormal metabolic states following TBI which have been categorized using cerebral microdialysis-derived combinations of parameters, and their evolution over time.

Specifically, this review addresses the following questions:

- Do studies using cerebral microdialysis classify abnormal metabolic states after TBI based on CMD data?
- What are the abnormal metabolic states following TBI, classified using cerebral microdialysis?
- Have the cerebral microdialysis-driven classifications of abnormal metabolic states following TBI changed over time?
- How do different classifications used to describe impaired cerebral metabolism following TBI overlap?

**Materials and Methods**

This systematic review was conducted using the methods outline in the Cochrane Handbook for Systematic Reviews\(^\text{10}\). Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines\(^\text{11}\).

**Protocol and registration**

The protocol for this review was published on PROSPERO, an international prospective register of systematic reviews\(^\text{12}\), on 27/01/2021 (PROSPERO registration number: CRD42021232365).

**Eligibility criteria**

The inclusion and exclusion criteria used in this review are presented in full in *Table 1*.

**Population and injury model**
Human studies in which patients had suffered traumatic brain injury, severe enough to require intubation, ventilation and invasive neuromonitoring, were the focus of this review. Studies involving animal models or non-traumatic brain injury were excluded.

**Intervention and Outcomes**

Studies were included if cerebral microdialysis was used to monitor cerebral metabolic parameters such as lactate, pyruvate, lactate/pyruvate ratio, glucose, glutamate and glycerol. Studies that did not utilize cerebral microdialysis were excluded. Similarly, studies which utilized microdialysis to measure non-metabolic parameters e.g. cytokine concentrations, drug concentrations or tau protein concentrations were excluded. Studies were not excluded based on the duration or frequency of cerebral microdialysis.

**Information sources**

To identify articles, a systematic search was performed on the MEDLINE and Embase databases on April 20th 2022.

**Search**

The terms used to search MEDLINE and Embase are described in Table 2. The final search was performed using the Ovid platform, utilizing the tool allowing searching multiple databases simultaneously. Articles in English were selected; no additional search limits were applied.

**Study selection**

Duplicates were identified and removed in Ovid using the in-built deduplication function. Following removal of duplicates, each of the titles and abstracts was screened independently by two of the authors (SV, FB) using the Rayyan software package13. Full-text review of the selected studies was subsequently performed independently by two reviewers (SV, FB) before combining the two ratings. Disagreements were resolved through discussion between the reviewers until mutual agreement was reached.

**Data Extraction and Synthesis**

Data were extracted using a custom-made data extraction sheet. Data points extracted were author, year of publication, country and center in which the study was conducted, study
characteristics (e.g. study design), sample characteristics (e.g. population size, age, GCS range of participants, TBI severity), intervention (e.g. location of microdialysis probe), the metabolic parameters measured, the cutoff values used to define normal and abnormal values for the different metabolic parameters (such as the LPR), and the nature of any neurometabolic groups which were identified.

For all the studies that were included, data extraction was performed by one author (SV). A subset of 10 studies (20% of the total) were randomly selected (using a random-number generator in R) to undergo data extraction by a second author (FB), to confirm inter-rater reliability. The agreement between the two independent data extraction processes was excellent with no conflicts.

No quantitative analysis (meta-analysis) was performed, because the aim of this review was to assess classification systems.

Quality of the evidence and risk of bias

Risk of bias and methodological quality were assessed with a custom-made quality assessment tool based on the Critical Appraisal Skills Program (CASP) checklists for observational studies, to include items specific to the research question\(^\text{14}\). The custom-made checklist is available in Appendix 1 (Supplemental material). This risk of bias assessment was applied to the studies describing abnormal metabolic states included in the full analysis. Overall, quality ratings were assigned to each study as follows:

- “No” ratings in any domain, or more than two “unclear” ratings → poor quality
- Maximum of two “unclear” ratings → fair quality
- Maximum of one “unclear” rating → good quality.

The Grading of Recommendation Assessment Development and Education (GRADE) criteria were used to assess the level of evidence for the metabolic state classifications identified\(^\text{15}\).

The GRADE classification is split into four levels: high - representing high evidence with multiple high-quality studies with consistent results, moderate - representing moderate evidence with one high-quality study or multiple low-quality studies, low - representing low evidence with one or more studies with severe limitations, and very low - representing very low evidence based on expert opinion or few studies with severe limitations.

Results

Search results and study selection
The search strategy produced a total of 825 individual studies, after duplicates were removed. After initial screening of titles and abstracts, 199 studies underwent full-text review. Of these, 53 records were included in this review\textsuperscript{8,16–66}. The PRISMA Flow diagram summarizing this is presented in figure 1, including reasons for exclusion of articles read as full text.

**Study characteristics**

All 53 studies were observational, with the majority (45/52) performed prospectively. Summary details of all 53 studies are included in Appendix 2 (Supplemental Material). These 53 studies were conducted across 11 countries and 21 individual institutions. The population size varied widely across studies, from 5 to 619\textsuperscript{37,57,58,65}. In total, this comprised 3211 TBI patients. All studies included patients with moderate-severe TBI, identified as either a GCS of less than 8, or a higher GCS with imaging finding consistent with severe brain injury, such as diffuse axonal injury, mass effect with midline shift, large intracranial hematomas, or cerebral edema.

**Identifying abnormal metabolic states: synthesis of the results**

Fourteen studies described abnormal metabolic states based on inclusion of cerebral microdialysis parameters\textsuperscript{21,22,25,27,30,39,45,50,51,54,57,62,65,66}. These studies were therefore included in the next data synthesis steps. Together, these studies had a total population of 1582 TBI patients.

**CMD probe location, sampling technique and timing of monitoring**

Most of the studies described the location used for the CMD probe in their subjects (51/53). The most common location for the CMD probe was the right frontal lobe, used in 35 studies, aiming for macroscopically normal brain. Thirteen studies placed the CMD probe in the penumbra of a focal lesion (perilesional). Three studies had two CMD probes inserted in all subjects, one in the penumbra of a focal lesion and one in healthy-looking brain. When looking specifically at the 14 studies describing abnormal metabolic states, variation in probe location remained: 8 specified a right frontal location in macroscopically normal brain; 3 were perilesional; one was ipsilateral to the injured hemisphere; and two had unspecified parenchymal locations.

With one exception (Bullock et al)\textsuperscript{21}, the studies that we reviewed described hourly sampling of microdialysate, conferring a degree of standardization across sampling techniques. CMD
sampling frequency is relevant because longer sampling periods would potentially result in less granular data. Studies primarily monitored patients for the first few days following TBI, with many starting on the day of the injury itself. Five studies specifically reported that monitoring started on day 0 from injury. The minimum reported period of monitoring was at least 12 hours, with several studies reporting a monitoring duration in the range of 3-5 days from injury. Only one study, by Svedung Wettervik et al., stipulated a longer 10-day monitoring period.

Classifications of abnormal metabolic states
Details of the parameters used in the classifications included in the 14 studies are summarized in Table 3. Marked differences regarding terminology and definitions of metabolic states existed across studies, as described later in this section.

Most studies used CMD parameters alone to define abnormal metabolic categories; figure 2 below summarizes how the classification systems in different papers overlap with each other.

Some studies used additional parameters from other modalities in combination with CMD metrics. For example, Hlatky et al. combined PbtO2 readings with CMD to identify hypoperfusion. Marini et al. described metabolic states as well as cerebral blood flow abnormality states based on CPP and cerebral oxygen extraction measured through near infrared spectroscopy. Severe metabolic crisis was associated with type 2 flow abnormality (CPP >60 mmHg with PbtO2 <20 mmHg), likely due to ischemia as the underlying pathology.

Sala et al. investigated cerebral lactate metabolism using CMD and PbtO2 monitoring. Most episodes of raised lactate concentration were associated with glycolysis and normal PbtO2, rather than with hypoxia. Perfusion CT scans were also obtained. Glycolytic lactate was associated with normal or supranormal brain perfusion, whereas hypoxic lactate was associated with globally reduced perfusion of brain.

Svedung Wettervick et al. investigated the relationship between arterial oxygenation (pO2) and cerebral metabolism following TBI. Pattern A ("energy metabolic disturbances, limited substrate supply") was associated with lower pO2 values (p<0.001). Higher mean arterial pO2 was associated with lower CMD lactate levels, and, in cases of limited pyruvate supply, arterial pO2 was higher where oxidative metabolism was preserved (normal LPR).
Vespa et al. combined CMD metabolites’ data with PET imaging to study the cause of metabolic crisis\textsuperscript{66}. \textit{Metabolic crisis} was defined as an LPR >40, whereas \textit{ischemia} was described as LPR >40 with cerebral glucose <0.2 mmol/L, or as an oxygen extraction fraction (OEF) >0.75 using PET criteria. Metabolic crisis occurred in 25\% of monitoring, but ischemia only occurred in 2.4\% using CMD parameters and in 1\% using PET criteria. Combining this with PET parameters, LPR correlated negatively with the cerebral metabolic rate of oxygen (CMRO\textsubscript{2}).

Nordstrom et al. noted that the mitochondrial dysfunction pattern was more common than the ischemic pattern\textsuperscript{45}. They also studied biochemical patterns in relation to TBI lesions. Patients with extradural hematomas and no mass lesion were more likely to have normal LPR, whereas patients with subdural hematomas or hemorrhagic contusions had higher LPR values\textsuperscript{45}.

\textit{Relation to outcomes}

Twenty-seven studies described how monitoring parameters relate to outcome. A range of clinical outcome measures were addressed. These included mortality (8 studies), favorable or unfavorable outcome described by the Glasgow Outcome Score (GOS) (13 studies), presence of spreading depolarization (1 study), and development of frontal lobe atrophy (1 study).

Of the 14 studies classifying abnormal metabolic states, 7 assessed correlations with outcome. Bullock et al. and Chamoun et al. showed that raised glutamate was associated with poor functional neurological outcome and increased mortality\textsuperscript{21,22}. Eiden et al. identified a ‘healthier’ metabolic pattern characterized by higher levels of CMD lactate, pyruvate and glucose, and lower levels of glutamate and ICP, a pattern which was associated with better functional outcomes (Glasgow Outcome Scale Extended) at 6 months\textsuperscript{25}.

Gupta et al. studied CMD parameters in patients with severe TBI who had undergone decompressive craniectomy\textsuperscript{27}. Patients with poor outcomes (measured as GOS at 6 months) had higher proportion of both mitochondrial dysfunction (LPR >25 and pyruvate >70 \textmu mol/L) and ischemia (LPR >25 and pyruvate <70 \textmu mol/L) (p<0.001) compared to those with favorable outcome.

Marini et al. also found an association between metabolic crisis and higher likelihood of non-survival\textsuperscript{39}. 
Stein et al. showed that metabolic crisis (LPR >25 and glucose <0.8 mmol/L) was common, seen in 74% of their patients, despite normal ICP. Moreover, patients with unfavorable outcome (GOS-E ≤ 6 at 6 months) spent longer in the state of metabolic crisis (p = 0.011). Timofeev et al. addressed how cerebral hypoxia and acidosis relate to mortality in TBI and to disturbances of cerebral metabolism. Four states were described based on PbtO2 and cerebral extracellular pH (pHbt). State 1 showed low PbtO2 and low pHbt, state 2 had normal PbtO2 and low pHbt, state 3 was characterized by low PbtO2 and normal pHbt, and state 4 with normal PbtO2 and normal pHbt. State 2 was associated with the highest levels of LPR, lactate and glucose, whereas state 1 showed high LPR with reduced glucose (p<0.001). State 2 was also associated with the highest mortality (p=0.021).

Guilfoyle et al. found that raised LPR in days 3 – 7 after injury was more likely in the poor outcome group, and that high LPR was an independent predictor of ordinal clinical outcome 7 months post-injury, dichotomized into favorable (Glasgow Outcome Scale 4-5) and unfavorable (GOS 1-3). Moreover, the relationships between LPR and CPP< PbtO2 and brain glucose directly suggest therapeutic goals that could be adopted to improve cerebral metabolism.

Analysis of risk of bias
Risk of bias assessment was performed for the 14 studies that described abnormal metabolic states, as these were included in the amalgamation of the evidence. A custom-made risk of bias assessment (Appendix 1) was used, and the results are summarized in Table 4 below. Methodological quality was overall good across the studies, with the majority describing clear methodology. The main area prone to bias was the lack of clear description if confounding factors and measures taken to account for these. Additionally, in a number of studies, a detailed description of how the subjects were recruited could have been strengthened, specifically with regards to whether all consecutive eligible patients were included or whether another method to obtain the patient sample was used (e.g. random sample). Importantly, follow-up was reported as complete (greater than 85%) in all 14 studies. This is especially relevant to evaluation of outcome, as incomplete follow-up may introduce bias.

GRADE: level of evidence
GRADE ratings were used to evaluate the quality of evidence for each of the main metabolic abnormalities described across the included studies, namely: metabolic crisis, ischemia, mitochondrial dysfunction. These are summarized as follow in Table 5.

Discussion

Of the 53 studies identified in this review as using CMD monitoring in TBI patients, only 15% (14 studies) described classifications of abnormal metabolic states based on CMD parameters, sometimes in conjunction with other monitoring modalities.

Are the classifications describing the same phenomena?

To evaluate if there is significant overlap across the classifications described in the studies included in this review, it is important to consider how energy generation occurs in the brain. Glucose is the preferred energy substrate for neurons through the process of glycolysis, although neurons can also utilize lactate as a substrate through the astrocyte-neuron lactate shuttle (ANLS)\(^6\). In aerobic conditions, for every molecule of glucose metabolized via the three-stage pathway of glycolysis, TCA cycle and electron transport chain, the theoretical maximum overall yield is 36-38 molecules of ATP, but the actual yield is considered somewhat lower\(^6\). Under anaerobic conditions, or in cases of mitochondrial dysfunction, pyruvate is converted to lactate by the enzyme lactate dehydrogenase (LDH) in the cytosol, instead of entering the mitochondrial TCA cycle. This shift increases the lactate/pyruvate ratio (LPR), which is a measure of the metabolic redox state.

The above processes are summarized in figure 3, reproduced from Carpenter et al\(^6\).

Pathological conditions relevant to patients with TBI, including cerebral ischemia that can arise in the context of raised intracranial pressure, altered cerebral autoregulation, or insufficient oxygen supply affect these metabolic processes. Inadequate energy substrate supply such as scarcity of glucose can also contribute to abnormalities, and finally impaired utilization of the available energy substrates due to cellular damage can also occur.

The role of CMD probe location and monitoring timing

Cerebral microdialysis allows assessment of focal rather than global metabolism, making probe location an important factor for interpretation of results. For example, Timofeev et al. studied microdialysis catheter location, showing that decreases in perfusion and oxygenation were associated with deteriorating neurochemistry, and these effects were more pronounced...
in perilesional tissue and when cerebrovascular reactivity was impaired\textsuperscript{70}. Probe locations varied widely, and in a minority of studies multiple rather than single probes were used. Due to small numbers and heterogeneity, stratification for probe location was not possible for systematic comparison of metabolic states. In future work, separation between probes located in perilesional tissue versus “normal” brain should be adopted.

Timing and duration of monitoring is also relevant, on account of the dynamic nature of the pathophysiological processes occurring in the acute phase following TBI. Most studies included in this review monitored patients for the first 3-5 days following injury. In future work, it would be relevant to standardize monitoring protocols to assess different phases of metabolic derangement following initial injury and facilitate comparison across studies. For example, Guilfoyle et al. found a rising trend in LPR from 48 hours after TBI for up to two weeks, in patients undergoing prolonged monitoring\textsuperscript{65}. Further investigation of whether different metabolic patterns occur at pre-determined time points following injury, for example 24, 48, 72, 96 hours, would provide additional information on evolving abnormal metabolic processes.

\textit{Metabolic crisis}

Metabolic crisis is one of the commonly defined abnormal metabolic states in the studies included in this review\textsuperscript{39,54,66}. Metabolic crisis is used as a description of a state where the LPR is raised above normal values (>25, although higher cut-offs such as 40 have also been used). Metabolic crisis appears to be an umbrella descriptor, primarily defined by high LPR alone, and allowing for sub-categories depending on the cause of metabolic crisis identified, such as ischemia or mitochondrial dysfunction.

\textit{Classifications of ischaemia}

Ischemia is described by the papers included in this review as an abnormal metabolic state. Based on CMD parameters, ischemia definitions often include raised LPR values above 25 together with markers of “anaerobic” metabolism, such as low glucose levels\textsuperscript{30,66}, low pyruvate levels\textsuperscript{27,39,45}, or high lactate\textsuperscript{50,51}. Vespa et al. in 2005 discussed the incidence of ischemia post TBI is low both in terms of regional ischemia (CMD) and global ischemia (PET)\textsuperscript{66}. Although overt ischemia is uncommon with modern neurocritical care, microvascular ischemia has been evidenced by advanced imaging in some situations\textsuperscript{71,72}. The majority of metabolic crisis is non-ischemic
and as such LPR is a non-specific indicator of ischemia as it simply reflects an impaired redox state which may result from other mechanisms such as mitochondrial dysfunction.

Classifications of mitochondrial dysfunction

Mitochondrial dysfunction can be described as an abnormal metabolic state where there is impairment of the cell’s ability to utilize energy substrate such as glucose or pyruvate and oxygen, despite adequate supply.

There is some variation in the exact cut off used for normal values among the studies, but all the definitions of mitochondrial dysfunction identified use a raised LPR and a normal level of pyruvate. This is in keeping with a problem further downstream to the lack of energy substrate. This definition overlaps or coincides with Pattern C identified by Svedung Wettervik et al., described as abnormal metabolism with adequate pyruvate supply.

The role of energy substrates

Glucose was used in several classifications. Importantly, low CMD glucose is a feature of abnormal metabolic states, rather than high glucose. This reflects the primacy of glucose for neuronal energy generation in aerobic conditions. Furthermore, the goal directed avoidance of hyperglycemia in intensive care protocols avoids very high levels of systemic glucose which may be translate into raised CMD glucose.

Low glucose combined with high LPR was classified as ischemia by Vespa. Eiden noted that glucose was overall higher in the healthier metabolic pattern A, perhaps indicating preserved substrate supply. This is in line with the latest cerebral microdialysis consensus statements, where low brain glucose together with high LPR is suggested to signify ischemia and / or tissue hypoxia. High CMD glucose has also been associated with unfavorable outcome, as described in the same consensus statement. This seems to suggest that an optimal range for brain glucose exists, and deviation from this in either direction is undesirable in TBI. In healthy states, serum glucose concentration and control influence brain glucose, but evidence suggests this relationship may be lost in brain injury. For example, other secondary pathological phenomena occurring after TBI such as spreading depolarization may cause rapid reduction in brain glucose.

There is variation in the levels that have been described as normal for pyruvate, some studies using values around 70 μmol/L and other studies using higher cut off values around 120 μmol/L. There is no robust consensus on the threshold for normal pyruvate with wide

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801
ranges reported in the literature, adding to the heterogeneity in cut offs used. Further work to determine the best threshold would provide evidence to complement our understanding of normal values found within the brain. Additionally, as CMD is an invasive monitoring technique, there is little available data from normal human brain of individuals without brain injury. Authors often use non-lesion TBI brain for this, however this ignores the fact that there can be diffuse, widespread injury. Previous work using $^{31}$P MRS described that biochemical abnormalities exist in the absence of radiologically-visible injury based on conventional and advanced MRI. The few studies that included normal (non-TBI) brain performed CMD in normal-appearing brain tissue in patients undergoing surgery for benign tumours.

Despite this variation, there is agreement across the studies that the combination of high LPR and low pyruvate levels describe states of ischemia, whereas high LPR with normal or near normal pyruvate are in line with mitochondrial dysfunction or states with preserved substrate supply but impairment in substrate utilization.

The role of lactate in cerebral metabolism is yet to be fully understood, with evidence that it increases in states of injury and anaerobic metabolism, but it can also be a useful energy fuel for example through the ANLS. Using microdialysis delivery of $^{3-13}$C lactate in TBI patients, Gallagher et al. and Jalloh et al. showed that lactate was metabolized via the TCA cycle. Sahuquillo et al. used lactate in conjunction with LPR and identified two metabolic states with raised lactate >2.5 mM. High lactate and high LPR indicates anaerobic metabolism, whereas high lactate and normal LPR suggests aerobic hyperglycolysis.

Similarly, Sala et al. described a hypoxic lactate state characterized by high lactate and low brain tissue oxygen tension, and a glycolytic lactate state, where lactate is raised but with normal oxygenation and normal pyruvate levels. Finally, it should be remembered that pyruvate and lactate are not just produced by glycolysis. Pyruvate can also be a spin-out product of the TCA cycle (termed cataplerosis) and then either recycled (via acetate) back into the TCA cycle, or converted by lactate dehydrogenase into lactate that can exit the cell.

**Glutamate-based classifications**

Two papers used glutamate levels to determine metabolic states, indicating that higher or rising glutamate levels are associated with worse clinical outcomes, however this phenomenon was noted in isolation and not related to other CMD parameters. Raised glutamate may reflect a reduced capacity for astrocytic uptake at times of metabolic stress. Although these classification algorithms incorporate glutamate thresholds, this may reflect
the putative role of glutamate in excitotoxicity-induced injury, rather than a presumption that glutamate plays a role in energy generation directly.

No other papers focused on glutamate as a parameter to focus on for further classification, perhaps reflecting evidence from the latest cerebral microdialysis consensus meeting stating that other parameters (such as LPR, glucose) are more useful than glutamate in offering information on deranged metabolism\textsuperscript{73}. In a CMD study of 619 TBI patients, glutamate levels were generally higher in the unfavorable outcome group (vs. favorable outcome group), but not significantly different\textsuperscript{65}. Glutamate therefore does not appear to be a strong candidate for thresholding in classification algorithms.

The wider context

The results of this review were interpreted in the context of the latest cerebral microdialysis consensus statement published in 2015\textsuperscript{73}. From a methodological perspective, most papers adhered to the recommendations to describe the location of the CMD probe and data acquisition techniques. Abnormal threshold values exhibit some variation, but overall fall within the ranges described by the consensus statement.

In a review published in 2017, our group describes a stepwise approach to assess the etiology of raised LPR in TBI patients, summarized in Table 6\textsuperscript{83}. The monitoring parameters used (ICP, PRx, brain tissue oxygen, brain glucose concentration and LPR) help guide therapy and correct physiological abnormalities in a stepwise fashion.

Although multiple neurometabolic abnormalities can co-exist, it is important to identify the cases of mitochondrial dysfunction that are present despite implementation of standard neuro-intensive care intervention, as these instances are where novel therapeutic modalities are needed due to the lack of standard treatment.

More recently, the same algorithm was used to identify TBI patients showing the mitochondrial dysfunction pattern. In this group of patients, disodium 2,3-\textsuperscript{13}C\textsubscript{2} succinate was administered focally through the microdialysis catheter to five patients and resulted in a reduction in LPR, suggesting that exogenous succinate may represent a targeted intervention to treat mitochondrial dysfunction\textsuperscript{9}. Also, the \textsuperscript{13}C-labelling patterns in the metabolites indicated that TCA cycle metabolism of the 2,3-\textsuperscript{13}C\textsubscript{2} succinate occurred\textsuperscript{9}.

Limitations
The studies included were heterogeneous in several methodological aspects. Their standard procedures for multimodality monitoring varied; notably, CMD probes had heterogeneous locations. Although the majority were placed in the standard location of the right frontal lobe (often adjacent to ICP/PhbO2 monitors), some had other locations such as in the penumbra of a focal lesion, or ipsilateral to a mass lesion. As microdialysis samples local metabolism, probe location near to or away from a mass lesion could affect the values of CMD parameters sampled. Additionally, heterogeneity was present in the parameters used for classifications of abnormal brain metabolism, limiting the strength of the evidence for each individual parameter.

A second limitation was in the small population sizes in some of the included studies, with numbers ranging from as low as 19 to as many as 619. It is possible that some of the studies with small populations are under-powered, limiting the strength of their conclusions. All the studies included were observational in nature. Although observational studies can be perceived as having lower quality of evidence compared to randomized studies, they are powerful in describing the incidence or prevalence of pathophysiological states and are therefore appropriate for the research question of this review.

Future steps towards standardization
This review identifies steps that could be taken in future studies to achieve better standardization and more robust classification of abnormal metabolic states. Firstly, defining key time points to assess metabolic abnormalities would be important, to better evaluate and compare temporal changes occurring following injury. Secondly, agreement on threshold values for each parameter of interest is advised, to limit the heterogeneity seen in included studies (for example, cut-offs for abnormal pyruvate levels varied). Thirdly, clear description for CMD probe location in relation to the TBI present is important. Finally, adopting uniform outcome assessments would facilitate result pooling and correlation of abnormal metabolic states to clinical outcomes. Future prospective studies incorporating the above suggestions would facilitate strengthening of the evidence, with the aim to standardize abnormal metabolic states and plan targeted interventions that are reproducible, so that their impacts can be measured.

Overall, the results suggest that abnormal metabolism, defined as metabolic crisis, ischemia or mitochondrial dysfunction appears to be associated with worse outcome. Therefore,
therapeutic goals that could be adopted to improve cerebral metabolism should be a research focus.

Conclusions

This systematic review aimed to summarize the published literature on microdialysis-defined abnormalities of metabolic states following TBI. Among these reports describing cerebral microdialysis monitoring in TBI, a small number of studies formally attempted to classify abnormal metabolic states identified in their patient populations. This review confirmed that LPR >25 is consistently described as a reliable marker for abnormal cerebral metabolism, and that such elevated LPR can have several etiologies. The term “metabolic crisis” has been used to describe states of abnormal metabolism with raised LPR, but it is broad and can encompass ischemic metabolism, or substrate depletion, or mitochondrial dysfunction, depending on the classifications used. Combining LPR with other variables can categorize the abnormal states of ischemia and mitochondrial dysfunction. This review also identified the fact that there is still incomplete agreement on what parameters and cutoff values are best for the identification of different abnormal metabolic states. It also showed that combining CMD data with other monitoring modalities can offer more information on the etiologies of abnormal brain metabolism in the context of TBI. Finally, since the metrics of several classification algorithms overlap, a comparative study of the various methods can help to identify areas of common ground. The great advantage of LPR as a metric of energy failure is that it directly reflects the biochemical redox state within the brain. However, to target and direct appropriate therapies aimed at correcting such abnormalities, the underlying pathological state must be robustly identified, driving the need for accurate classification of metabolic abnormalities.
Authors’ Contributions

S.V. and A.H. designed the study protocol. S.V. and F.B. performed the screening, data extraction and manuscript writing processes. A.H., M.G., P.J.A.H. and K.L.H.C. critically revised the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

P.J.A.H. is a director of Technicam (Newton Abbot, UK), the manufacturer of the cranial access device used in several of the microdialysis studies cited in this article. The other authors have no conflict of interests to declare.

Funding acknowledgments

The authors disclose receipt of the following financial support for the research, authorship, and/or publication of this article: Medical Research Council (Grant no. G1002277 ID98489) and National Institute for Health and Care Research Biomedical Research Centre, Cambridge (Neuroscience Theme; Brain Injury and Repair Theme). Authors’ support; PJH–National Institute for Health Research and Care (Professorship, Biomedical Research Centre, Brain Injury MedTech Co-operative, Senior Investigator Award and the Royal College of Surgeons of England; KLHC–National Institute for Health and Care Research Biomedical Research Centre, Cambridge (Neuroscience Theme; Brain Injury and Repair Theme); AH–Medical Research Council/Royal College of Surgeons of England Clinical Research Training Fellowship (Grant no.G0802251), the NIHR Biomedical Research Centre and the NIHR Brain Injury MedTech Co-operative; SV-NIHR Academic Clinical Fellowship in Neurosurgery. The views expressed are those of the Authors and are not necessarily those of the NIHR or of the Department of Health and Social Care or of any of the other funding bodies.
References


Figure 1 - PRISMA Flow diagram, 2020 version. - Reason 1: not a full peer reviewed paper. This includes conference abstracts subsequently published as conference proceedings, conference abstracts for poster or oral presentations. (65)- Reason 2: wrong paper type. This represents review articles (3), case reports (2), technical papers (4) describing a technology. - Reason 3: not relevant as not including metabolic parameters. This describes studies using microdialysis to measure parameters such as cytokines but not the metabolic parameters stated in the inclusion criteria. (16)- Reason 4: not relevant as investigating the effect of specific interventions on microdialysis parameters. This includes the effect of interventions such as tight glucose control, temperature regulation, hyperoxia or use of antiepileptic medications. (49)- Reason 5: not relevant as using the wrong population type and wrong tissue sample. This includes studies including patients other than TBI patients, and those where tissue samples are other than monitoring brain parenchyma (e.g. CSF). (7)
Figure 2 - Schematic representation of how different classifications of abnormal metabolic states described in the articles included in this review overlap. The included studies are by Gupta et al.27, Marini et al.39, Nordstrom et al.45, Sahuquillo et al.50, Stein et al.54, Svedung Wettervik et al.62, Vespa et al.66.

940x529mm (72 x 72 DPI)
Figure 3 - schematic summary of energy metabolism in the brain, reproduced from Carpenter et al. 201465
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104x83mm (144 x 144 DPI)
Figure legends

**Figure 1** - PRISMA Flow diagram, 2020 version.

- **Reason 1:** not a full peer reviewed paper. This includes conference abstracts subsequently published as conference proceedings, conference abstracts for poster or oral presentations. (6559)
- **Reason 2:** wrong paper type. This represents review articles (32), case reports (2), technical papers (4) describing a technology.
- **Reason 3:** not relevant as not including metabolic parameters. This describes studies using microdialysis to measure parameters such as cytokines but not the metabolic parameters stated in the inclusion criteria. (165)
- **Reason 4:** not relevant as investigating the effect of specific interventions on microdialysis parameters. This includes the effect of interventions such as tight glucose control, temperature regulation, hyperoxia or use of antiepileptic medications. (496)
- **Reason 5:** not relevant as using the wrong population type and wrong tissue sample. This includes studies including patients other than TBI patients, and those where tissue samples are other than monitoring brain parenchyma (e.g. CSF). (7)

**Figure 2** - Schematic representation of how different classifications of abnormal metabolic states described in the articles included in this review overlap. The included studies are by Gupta et al\(^26\)\(^27\), Marini et al\(^38\)\(^39\), Nordstrom et al\(^45\)\(^44\), Sahuquillo et al\(^50\)\(^49\), Stein et al\(^54\)\(^53\), Svedung Wettervik et al\(^62\)\(^61\), Vespa et al\(^66\)\(^64\).

**Figure 3** - Schematic summary of energy metabolism in the brain, reproduced from Carpenter et al. 2014\(^65\) © 2014 The Authors. Published by Elsevier B.V. Open access under CC BY licence.
**Table 1. Inclusion and exclusion criteria**

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<th>Inclusion</th>
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<td>• Animal studies</td>
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<td><strong>Injury</strong></td>
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<td>• Non-traumatic brain injury</td>
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<td>• Subarachnoid haemorrhage</td>
<td>• Subarachnoid haemorrhage</td>
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<td><strong>Intervention</strong></td>
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<tr>
<td>• Multi-modality monitoring including cerebral microdialysis</td>
<td>• No use or description of cerebral microdialysis</td>
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<td><strong>Comparison</strong></td>
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<td>• None</td>
<td>• None</td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td>• Cerebral microdialysers used to measure metabolic parameters e.g.</td>
<td>• No use or description of microdialysis metabolic parameters e.g.</td>
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<td>• Lactate</td>
<td>• Cytokines</td>
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<td>• Pyruvate</td>
<td>• Drug concentrations</td>
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<td>• Glucose</td>
<td>• Tau protein levels</td>
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<td>• Glutamate</td>
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<td>• Glycerol</td>
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<td>Observational studies</td>
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**Table 2. Search strategy**

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<td>1 Traumatic brain injury.mp</td>
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</tr>
<tr>
<td>2 Tbi.mp</td>
<td>04/2022</td>
</tr>
<tr>
<td>3 Microdialysis.mp</td>
<td></td>
</tr>
<tr>
<td>4 Lpr.mp</td>
<td></td>
</tr>
<tr>
<td>5 Brain injuries, Traumatic/ (focussed to include traumatic injuries only)</td>
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<tr>
<td>6 1 or 2 or 5</td>
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<td>7 3 or 4</td>
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<td>8 6 and 7</td>
<td></td>
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<tr>
<td>9 Remove duplicates from 8</td>
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</table>

119386112447 2472975705 4059240596 4458711589 5402055072 428756136082 5196851978 44741211 789825
### Table 3 - summary of studies describing metabolic states on the basis of CMD parameters or multi-modality monitoring parameters

<table>
<thead>
<tr>
<th>Author (year, location)</th>
<th>Population size</th>
<th>CMD probe location</th>
<th>CMD samples</th>
<th>LPR cut-off</th>
<th>Monitored parameters</th>
<th>CMD sampling technique</th>
<th>CMD sampling timing</th>
<th>Metabolic states described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullock (1998, United States)</td>
<td>80</td>
<td>Peri-lesional if focal lesion present</td>
<td>-</td>
<td>-</td>
<td>CMD: glutamate, aspartate, threonine ICP</td>
<td>-</td>
<td>Day 0-4 from TBI</td>
<td>Low glutamate (&lt;5 μmol/L)</td>
</tr>
<tr>
<td>Chamoun (2010, United States)</td>
<td>165</td>
<td>Parenchymal next to PbtO2 probe</td>
<td>-</td>
<td>-</td>
<td>CMD: glutamate ICP, PbtO2</td>
<td>-</td>
<td>Ho urnal sampling, Per fusate 3μl/min</td>
<td>Pattern 1: glutamate normalises within 120 hours</td>
</tr>
<tr>
<td>Eiden (2019, Switzerland)</td>
<td>38</td>
<td>Visually normal brain</td>
<td>-</td>
<td>-</td>
<td>CMD: lactate, pyruvate, glucose, glutamate, ketones ICP, PbtO2</td>
<td>-</td>
<td>Dur ation unspecified</td>
<td>Metabolic state A (healthier): higher lactate, pyruvate, glucose, ketones, lower glutamate and ICP</td>
</tr>
<tr>
<td>Guilfoyle (2021, United Kingdom)</td>
<td>619</td>
<td>Right frontal</td>
<td>56307</td>
<td>25</td>
<td>CMD: lactate, pyruvate, glucose, glutamate, glycerol ICP, PbtO2, CPP</td>
<td>Hourly sampling, Per fusate 0.3μl/min</td>
<td>Median time to initiation 26.9 hrs, Median duration 4.8 days [2.7 – 7.8 IQR]</td>
<td>Ischaemia / hypoxia: LPR &gt;25, CPP &lt;60 mmHg, PbtO2 &lt;18 mmHg</td>
</tr>
<tr>
<td>Gupta (2017, India)</td>
<td>41</td>
<td>Ipsilateral to the injured hemisphere</td>
<td>3813</td>
<td>25</td>
<td>CMD: lactate, pyruvate, glucose</td>
<td>Hourly sampling, Per fusate 0.3μl/min</td>
<td>Staring day of injury, Duration 3-5 days</td>
<td>Ischaemia: LPR &gt;25, pyruvate &lt;70</td>
</tr>
<tr>
<td>Study</td>
<td>Period</td>
<td>Location</td>
<td>Methodology</td>
<td>Sampling Duration</td>
<td>Thresholds</td>
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<tr>
<td>Hlatky (2004, United States)</td>
<td>30</td>
<td>Peri-lesional</td>
<td>CMD: lactate, pyruvate, glucose, glutamate ICP, PbtO2</td>
<td>Hourly sampling</td>
<td>Hypoperfusion: PbtO2 &lt;10, low glucose &lt;1, high lactate &gt;4 and high glutamate, inconsistent pyruvate</td>
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<tr>
<td>Marini (2020, United States)</td>
<td>29</td>
<td>Unclear location.</td>
<td>CMD: lactate, pyruvate, glucose ICP, PbtO2, NIRS</td>
<td>Hourly sampling</td>
<td>Metabolic crisis if LPR &gt;25:</td>
<td></td>
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<tr>
<td>Nordstrom (2016, Sweden)</td>
<td>213</td>
<td>Biochemical penumbra if focal lesion, next to ventricular catheter if diffuse. Some patients had 2 probes, one in normal tissue</td>
<td>CMD: lactate, pyruvate, glucose, glutamate, glycerol ICP, CPP</td>
<td>Hourly sampling</td>
<td>Ischaemia: LPR&gt;30 and pyruvate &lt;70</td>
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<tr>
<td>Sahuquillo (2014, Spain)</td>
<td>46</td>
<td>In macroscopically normal brain</td>
<td>CMD: lactate, pyruvate, glucose -</td>
<td>At least 12 hours</td>
<td>Pattern 1 (normal metabolism): lactate ≤2.5 and LPR&lt;25</td>
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<tr>
<td>Sala (2013, Switzerland)</td>
<td>24</td>
<td>Normal brain parenchyma (21/24), peri-</td>
<td>CMD: lactate, pyruvate, glucose, glutamate</td>
<td>Hourly sampling</td>
<td>Pattern 2 (aerobic hyperglycolysis): lactate &gt;2.5 and LPR&lt;25</td>
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<td>Pattern 3 (anaerobic metabolism): lactate &gt;2.5 and LPR&gt;25</td>
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<td>Pattern 4 (low pyruvate): lactate ≤2.5 and LPR&gt;25</td>
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<td>Glycolytic lactate: lactate &gt;4, PbtO2 normal, pyruvate &gt;119</td>
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<td>Hypoxic lactate: lactate &gt;4, low PbtO2</td>
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<tr>
<td>Source</td>
<td>Region</td>
<td>CMD Parameters</td>
<td>PbTO2</td>
<td>Perfusion</td>
<td>Duration</td>
<td>Observations</td>
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<tr>
<td>Stein (2012, United States)</td>
<td>Right frontal</td>
<td>lactate, pyruvate, glucose, glutamate</td>
<td>0.3 μl/min</td>
<td>Hourly sampling, perfusate</td>
<td>5 days from TBI</td>
<td>Metabolic crisis: glucose &lt;0.8 and LPR &gt; 25</td>
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<tr>
<td>Svedung Wettervik (2020, Sweden)</td>
<td>Right frontal</td>
<td>lactate, pyruvate, glucose, glutamate</td>
<td>0.3 μl/min</td>
<td>Hourly sampling, perfusate</td>
<td>72 hours from TBI</td>
<td>Pattern A: Energy metabolic disturbance and limited pyruvate supply: LPR&gt;25, pyruvate &lt;120μM</td>
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<td>PaO2</td>
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<td>Pattern B: No metabolic disturbance and adequate substrate: LPR&lt;25, pyruvate&gt;120μM</td>
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<td>Pattern C: Metabolic disturbance with adequate substrate: LPR&gt;25, pyruvate&gt;120μM</td>
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<td>Pattern D: No metabolic disturbance and limited pyruvate supply: LPR&gt;25, pyruvate &lt;120μM</td>
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<tr>
<td>Timofeev (2013, United Kingdom)</td>
<td>Right frontal</td>
<td>lactate, pyruvate, glucose, glutamate glycerol</td>
<td>0.3 μl/min</td>
<td>Hourly sampling, perfusate</td>
<td>72 hours from TBI</td>
<td>State 1 (ischaemia, hypoxia): low PbtO2 and pHbt (LPR and lactate high, glycerol and glucose low)</td>
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<td>PbtO2, pHbt</td>
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<td>State 2 (acidosis without hypoxia): normal PbtO2, low pHbt</td>
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<td>State 3: low PbtO2, normal pHbt</td>
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<td>State 4: normal PbtO2 and PbtO2</td>
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<tr>
<td>Vespa (2005, United States)</td>
<td>Adjacent to ventriculostomy (right frontal)</td>
<td>lactate, pyruvate, glucose, glutamate glycerol</td>
<td>2 μl/min</td>
<td>Hourly sampling, perfusate</td>
<td>Starting on day 0, all monitored until 36</td>
<td>Metabolic crisis: LPR&gt;40</td>
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<td>Ischaemia: LPR&gt;40 and glucose &lt;0.2 mmol/L</td>
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</table>
| Legend: NIRS = near infrared spectroscopy; ICP = intracranial pressure; CPP = cerebral perfusion pressure, PET = positron emission tomography; CMRO2 = cerebral metabolic rate of oxygen; CBF = cerebral blood flow, OEF = oxygen extraction fraction; pHbt = pH of brain tissue, PbtO2 = brain tissue oxygen tension.  
| ICP, PbtO2, CPP, PET (CMRO2, CBF, OEF) | hours from TBI, unclear full duration |
**Table 4 - Risk of bias assessment for studies describing classifications of abnormal metabolic states.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Q1</th>
<th>Q2</th>
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<tr>
<td>Marini et al. 39 38</td>
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<td>Nordstrom et al. 45 44</td>
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<td>Sahuquillo et al. 50 49</td>
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<td>Sala et al. 51 50</td>
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<td>Stein et al. 54 53</td>
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<td>Svedung Wettervik et al. 57 56</td>
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<td>Timofeev et al. 58</td>
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<td>Vespa et al. 66</td>
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<td>Fair</td>
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</table>

Legend: green = yes, low risk; red = no, high risk; amber = uncertain, unclear risk.
<table>
<thead>
<tr>
<th>Metabolic abnormality</th>
<th>Parameters</th>
<th>GRADE certainty of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic crisis</td>
<td>LPR &gt;25</td>
<td><em>Moderate</em> due imprecision</td>
<td>Consistent results across observational studies, however cut off values vary</td>
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<tr>
<td>Ischaemia</td>
<td>LPR &gt; 25 and markers of anaerobic metabolism (e.g. low glucose, or low pyruvate)</td>
<td><em>Low</em> due to imprecision and inconsistency</td>
<td>Markers of anaerobic metabolism vary across studies</td>
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<tr>
<td>Mitochondrial dysfunction</td>
<td>LPR &gt;25 and normal substrate levels (e.g. pyruvate)</td>
<td><em>Low</em> due to imprecision and inconsistency</td>
<td>Cut off values and exact substrate measures vary across studies</td>
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</tbody>
</table>

*Table 5* - GRADE level of evidence.
Table 6 - Algorithm used to classify pathological states for LPR > 25, with monitoring-targeted interventions to correct abnormalities, from Thelin et al. 2017.

<table>
<thead>
<tr>
<th>Abnormal state</th>
<th>ICP mmHg</th>
<th>PRx (auto-regulation)</th>
<th>PbtO2 (mmHg)</th>
<th>Brain glucose (mmol/L)</th>
<th>Treatment target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hypertension</td>
<td>&gt;20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Several, such as: increasing sedation, hyperosmolar therapy, ICP algorithm</td>
</tr>
<tr>
<td>Delivery failure</td>
<td>&lt;20</td>
<td>&gt;0.3</td>
<td>-</td>
<td>-</td>
<td>Increase CPP</td>
</tr>
<tr>
<td>Diffusion barrier</td>
<td>&lt;20</td>
<td>&lt;0.3</td>
<td>&lt;15</td>
<td>-</td>
<td>Increase FiO2</td>
</tr>
<tr>
<td>Neuroglycopenia</td>
<td>&lt;20</td>
<td>&lt;0.3</td>
<td>&gt;15</td>
<td>&lt;1.0</td>
<td>Increase systemic glucose</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>&lt;20</td>
<td>&lt;0.3</td>
<td>&gt;15</td>
<td>&gt;1.0</td>
<td>No standard treatment available</td>
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</table>
### Appendices

#### Appendix 1 - Quality assessment checklist created for this study

<table>
<thead>
<tr>
<th>Questions</th>
<th>Yes</th>
<th>No</th>
<th>Can’t tell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. Was the study designed to evaluate the use of cerebral microdialysis in classifying abnormal metabolic states after TBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2. Was this an observational study where CMD monitoring data was used (on its own or as part of multi-modality monitoring)?</td>
<td></td>
<td></td>
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<tr>
<td>Q3. Were the subjects recruited in an acceptable way? <em>Selection bias kept to a minimum (e.g. all consecutive admitted patients with severe TBI)</em></td>
<td></td>
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<tr>
<td>Q4. Were all severe TBI patients identified through imaging and/or clinical examination?</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Q5. Was there an acceptable description of the monitoring methods used in the subjects (e.g. ICP monitor, brain tissue oxygen tension monitor, CMD)?</td>
<td></td>
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</tr>
<tr>
<td>Q6. Was there a description of the CMD probe location?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q7. Was there a description of the thresholds used for abnormal values in monitored parameters (e.g. ICP &gt; 20 mmHg, LPR &gt; 25)?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q8. Was the outcome accurately measured to minimise bias?</td>
<td></td>
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<tr>
<td>Q9. Were confounding factors identified and discussed?</td>
<td></td>
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</tr>
<tr>
<td>Q10. Did the study provide classification of abnormal metabolic states based on measured parameters?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q11. Was the follow up of subjects complete enough? <em>Minimum of 85% of subjects complete follow up</em></td>
<td></td>
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</tr>
<tr>
<td>Q12. Were results described with adequate precision and was standard reporting with complete numbers (no unexplained missing data) available?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q13. Was there a discussion of how this study fits with other available evidence?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q14. Were the implications of this study for clinical practice discussed?</td>
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</table>
### Appendix 2 - details of all 52 studies included in the review

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Population size (number of patients)</th>
<th>GCS</th>
<th>TBI description</th>
<th>MD sample</th>
<th>Location of microdialysis probe</th>
<th>LPR cut-off</th>
<th>Microdialysis parameters</th>
<th>Other monitoring modalities used</th>
<th>Neuro-metabolic states described</th>
<th>Investigates correlation to outcome</th>
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</thead>
<tbody>
<tr>
<td>Adamides et al.</td>
<td>2009</td>
<td>Australia</td>
<td>prospective observational</td>
<td>14</td>
<td>≤ 9 (6.4 +/- 0.9)</td>
<td>severe TBI</td>
<td>1334</td>
<td>uninjured brain - contralateral to injury side or right frontal in diffuse injury</td>
<td>No absolute cut-off, increase &gt;20% from baseline</td>
<td>lactate, LPR, glycerol</td>
<td>ICP</td>
<td>No</td>
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<tr>
<td>Asgari et al.</td>
<td>2011</td>
<td>United States</td>
<td>prospective observational</td>
<td>19</td>
<td>severe TBI</td>
<td>2261</td>
<td>na</td>
<td>None</td>
<td>LPR</td>
<td>ICP</td>
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<td></td>
<td></td>
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<tr>
<td>Asgari et al.</td>
<td>2013</td>
<td>United States</td>
<td>prospective observational</td>
<td>30</td>
<td>severe TBI</td>
<td>4316</td>
<td>adjacent to ventriculostomy</td>
<td>25 (40 is also used)</td>
<td>LPR</td>
<td>ICP</td>
<td>No</td>
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<tr>
<td>Belli et al.</td>
<td>2008</td>
<td>United Kingdom</td>
<td>prospective observational</td>
<td>25</td>
<td>between 3 - 15</td>
<td>severe TBI</td>
<td>2102</td>
<td>in penumbra of focal lesion, or right frontal in diffuse injury</td>
<td>25</td>
<td>LPR, glutamate, glycerol</td>
<td>ICP</td>
<td>Yes</td>
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<td>Belli et al.</td>
<td>2006</td>
<td>United Kingdom</td>
<td>prospective observational</td>
<td>19</td>
<td>between 3 - 15</td>
<td>severe TBI</td>
<td>None</td>
<td>in penumbra of focal lesion, or right frontal in diffuse injury</td>
<td>None</td>
<td>lactate, pyruvate, glycerol, glutamate, NAA (n-acetylaspartate)</td>
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<tr>
<td>Bullock et al.</td>
<td>1998</td>
<td>United States</td>
<td>prospective observational</td>
<td>80</td>
<td>between 3 - 15</td>
<td>severe TBI</td>
<td>None</td>
<td>peri-lesional if focal lesion</td>
<td>None</td>
<td>glutamate, aspartate, theonine</td>
<td>ICP</td>
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<tr>
<td>Last Name</td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Criteria for Severe TBI</td>
<td>Location of Parenchyma in Similar Position to PbtO2 Probe</td>
<td>Investigated Metabolites</td>
<td>Interventions</td>
<td>ICP Monitoring</td>
<td>Results</td>
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<tr>
<td>Chamoun et al.</td>
<td>2010</td>
<td>United States</td>
<td>Prospective observational</td>
<td>165</td>
<td>&lt;= 8</td>
<td>Severe TBI</td>
<td>Parenchyma in similar position to PbtO2 probe</td>
<td>None</td>
<td>Glutamate</td>
<td>ICP, PbtO2</td>
<td>Yes</td>
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<tr>
<td>Clausen et al.</td>
<td>2005</td>
<td>United States</td>
<td>Prospective observational</td>
<td>76</td>
<td>&lt; 9</td>
<td>Severe TBI</td>
<td>Uninjured brain</td>
<td>None</td>
<td>Glycerol</td>
<td>PbtO2, CPP</td>
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<tr>
<td>Clausen et al.</td>
<td>2005</td>
<td>United States</td>
<td>Prospective observational</td>
<td>151</td>
<td>&lt; 9</td>
<td>Severe TBI</td>
<td>Uninjured brain - often right frontal</td>
<td>None</td>
<td>Lactate</td>
<td>PbtO2, CO2, pH</td>
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<td>Eiden et al.</td>
<td>2019</td>
<td>Switzerland</td>
<td>Retrospective (cohort 1) and prospective (cohort 2)</td>
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<td>&lt; 9</td>
<td>Severe TBI</td>
<td>None</td>
<td>Lactate, pyruvate, glucose, glutamate, ketones</td>
<td>ICP, PbtO2</td>
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<td>Engstrom et al.</td>
<td>2005</td>
<td>Sweden</td>
<td>Prospective observational</td>
<td>22</td>
<td>8 or less, motor score &lt; 5</td>
<td>Severe TBI</td>
<td>One in penumbra, one in normal tissue (ipsilateral or contralateral)</td>
<td>None</td>
<td>Lactate, pyruvate, glucose, glutamate, glycerol</td>
<td>ICP, PbtO2</td>
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<td>Guilfoyle et al.</td>
<td>2021</td>
<td>United Kingdom</td>
<td>Prospective observational</td>
<td>Between 3 - 15 Severe TBI</td>
<td>56307</td>
<td>Right frontal</td>
<td>Lactate, pyruvate, glucose, glutamate</td>
<td>ICP, PbtO2</td>
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<td>Gupta et al.</td>
<td>2017</td>
<td>India</td>
<td>Prospective observational</td>
<td>Median 7 (4, 7)</td>
<td>Severe (GCS &lt;= 8), post DC for refractory high ICP</td>
<td>Ipsilateral to injured hemisphere</td>
<td>Lactate, pyruvate, glucose</td>
<td>PbtO2, CPP</td>
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<td>Hejcl et al.</td>
<td>2011</td>
<td>Czech Republic</td>
<td>Prospective observational</td>
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<td>&lt;= 8</td>
<td>Severe TBI</td>
<td>Ipsilateral to injured hemisphere</td>
<td>Lactate, pyruvate, glucose, glutamate</td>
<td>ICP, CPP, PbtO2</td>
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<tr>
<td>Authors</td>
<td>Year</td>
<td>Country</td>
<td>Study Type</td>
<td>N</td>
<td>Age group</td>
<td>Location of injury</td>
<td>Severity</td>
<td>18F</td>
<td>Location of electrode</td>
<td>Methodology</td>
<td>Monitoring Methodology</td>
<td>ICP, PbtO2</td>
<td>3-13 C Lactate</td>
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<td>Hinzman et al.</td>
<td>2016</td>
<td>United States</td>
<td>prospective observation</td>
<td>16</td>
<td>&lt;9</td>
<td>severe TBI</td>
<td>1214</td>
<td>40</td>
<td>lactate, pyruvate, glucose, glutamate</td>
<td>electrode for SD</td>
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<td>Hlatky et al.</td>
<td>2004</td>
<td>United States</td>
<td>prospective observation</td>
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<td>&lt;9</td>
<td>severe TBI</td>
<td>peri-lesional</td>
<td>None</td>
<td>lactate, pyruvate, glucose, glutamate</td>
<td>ICP, PbtO2</td>
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<td>Hu et al.</td>
<td>2013</td>
<td>United States</td>
<td>prospective observation</td>
<td>30</td>
<td>&lt;9</td>
<td>severe TBI</td>
<td>adjacent to ventriculostomy</td>
<td>25</td>
<td>lactate, pyruvate</td>
<td>ICP</td>
<td>No</td>
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<td>United Kingdom</td>
<td>prospective observation</td>
<td>30</td>
<td>between 3 - 13</td>
<td>severe TBI</td>
<td>right frontal</td>
<td>None</td>
<td>glucose, lactate, pyruvate, glutamate</td>
<td>PET (CMRgluc)</td>
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<td>Isarashi et al.</td>
<td>2017</td>
<td>Japan</td>
<td>prospective observation</td>
<td>17</td>
<td>7 (IQR 3.8 - 7)</td>
<td>severe TBI (focal)</td>
<td>white matter at 1-2cm from surface, where haematoma removed</td>
<td>40 (cut-off identified retrospectively)</td>
<td>glucose, lactate, pyruvate, glutamate, glycero</td>
<td>LPR, LGR</td>
<td>No</td>
<td>No</td>
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<td>Jalloh et al.</td>
<td>2015</td>
<td>United Kingdom</td>
<td>prospective case control</td>
<td>30</td>
<td>&lt;= 8</td>
<td>severe TBI</td>
<td>right frontal, not within the lesion</td>
<td>None</td>
<td>glucose, lactate, pyruvate, glutamate, glycero</td>
<td>None</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Jalloh et al.</td>
<td>2018</td>
<td>United Kingdom</td>
<td>prospective case control</td>
<td>9 TBI, 5 control</td>
<td>severe TBI</td>
<td>right frontal, not within the lesion</td>
<td>None</td>
<td>glucose, lactate, pyruvate, glutamate</td>
<td>3-13 C Lactate</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Jalloh et al.</td>
<td>2013</td>
<td>United Kingdom</td>
<td>prospective observation</td>
<td>19</td>
<td>&lt;9</td>
<td>severe TBI (diffuse)</td>
<td>right frontal</td>
<td>None</td>
<td>glucose, lactate</td>
<td>arterial lactate conc</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Karathanos et al.</td>
<td>2011</td>
<td>Greece</td>
<td>prospective observation</td>
<td>38</td>
<td>&lt;9</td>
<td>severe TBI</td>
<td>normal brain parenchyma</td>
<td>25</td>
<td>glucose, lactate, pyruvate, glycero</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Mary Ann Liebert, Inc, 140 Huguenot Street, New Rochelle, NY 10801
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Age (Range)</th>
<th>Injury Location</th>
<th>Cytokines/Inflammation</th>
<th>Outcome 1</th>
<th>Outcome 2</th>
<th>Method 1</th>
<th>Method 2</th>
<th>Metabolites</th>
<th>Outcome 3</th>
</tr>
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<tbody>
<tr>
<td>Lakshmanan et al.</td>
<td>2010</td>
<td>United States</td>
<td>Prospective</td>
<td>5</td>
<td>&lt;9 or &lt;14</td>
<td>Severe TBI</td>
<td>Glucose, Lactate, Glutamate, Pyruvate, Glycerol</td>
<td>Proteome</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Marcoux et al.</td>
<td>2008</td>
<td>United States</td>
<td>Prospective</td>
<td>15</td>
<td>&lt;12</td>
<td>Severe TBI</td>
<td>Glucose, Lactate, Glutamate, Pyruvate, Glycerol</td>
<td>MRI Brain Volume at 6 Months</td>
<td>Yes</td>
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<tr>
<td>Marini et al.</td>
<td>2020</td>
<td>United States</td>
<td>Prospective</td>
<td>20</td>
<td>Median (3-5)</td>
<td>Severe TBI</td>
<td>Glucose, Lactate, Glutamate, Pyruvate</td>
<td>Yes</td>
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<td>Arterial Glucose Concentration</td>
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<tr>
<td>Meierhans et al.</td>
<td>2010</td>
<td>Switzerland</td>
<td>Prospective</td>
<td>20</td>
<td>&lt;9</td>
<td>Right Frontal</td>
<td>Glucose, Lactate, Glutamate, Pyruvate</td>
<td>No</td>
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<tr>
<td>Meierhans et al.</td>
<td>2012</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>26</td>
<td>&lt;= 8</td>
<td>Severe TBI</td>
<td>Glutamate, Pyruvate, Lactate, Glucose</td>
<td>Yes</td>
<td></td>
<td>ICP, MAP</td>
<td></td>
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<tr>
<td>Mellergard et al.</td>
<td>2012</td>
<td>Sweden</td>
<td>Prospective</td>
<td>69</td>
<td>&lt;9</td>
<td>None</td>
<td>Glucose, Lactate, Glutamate, Pyruvate, Glycerol</td>
<td>No</td>
<td></td>
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<tr>
<td>Nelson et al.</td>
<td>2004</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>26</td>
<td>&lt;9</td>
<td>Peri-lesional</td>
<td>Glucose, Lactate, Pyruvate, Glycerol</td>
<td>ICP, CPP</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Nelson et al.</td>
<td>2011</td>
<td>Sweden</td>
<td>Prospective</td>
<td>90</td>
<td>&lt;9</td>
<td>Peri-lesional</td>
<td>Glucose, Lactate, Pyruvate, Glycerol</td>
<td>ICP, CPP</td>
<td>Yes</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Design</td>
<td>n</td>
<td>&lt;9 (M &lt; 5)</td>
<td>Severe TBI</td>
<td>Observations</td>
<td>Biochemical Penumbra</td>
<td>Normal Tissue</td>
<td>glucose, lactate, glutamate, pyruvate, glycerol</td>
<td>ICP, CPP, PbtO2</td>
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</tbody>
</table>
| Nordstrom et al. 2016       | Sweden | prospective observation | 213 | <8 (M < 5) | severe TBI (4 groups: EDH, SDH, CHC - contusion, NFL - no focal lesion) | biochemical penumbra if focal lesion, next to ventricular catheter if diffuse. Some patients had 2 probes, one in normal tissue | 30 | glucose, lactate, glutamate, pyruvate, glycerol | ICP, CPP | Yes  
| Paraforou et al. 2011       | Greece | prospective observation | 34 | <9 | severe TBI | right frontal lobe if diffuse, ipsilateral frontal lobe if unilateral lesion | 25 (40 is also used) | glucose, lactate, glutamate, pyruvate, glycerol | ICP, CPP, PbtO2 | No  
| Patet et al. 2015           | Switzerland | retrospective analysis of prospectively recruited patients | 26 (18 TBI, 8 SAH) | <9 | severe TBI | normal brain parenchyma | 25 | glucose, lactate, glutamate, pyruvate, glycerol | ICP, CPP, PbtO2, arterial blood glucose | No  
| Purins et al. 2014          | Sweden | prospective observation | 23 | <9 | severe TBI | right frontal | None | glucose, lactate, glutamate, pyruvate, glycerol | ICP, CPP, PbtO2 | Yes  
| Reinert et al. 2000         | United States | prospective observation | 85 | <9 | severe TBI | right frontal | None | lactate, glutamate, potassium | ICP, CBF | No  
| Sahuquillo et al. 2014      | Spain | retrospective observation, subset of pre-existing dataset | 46 | Median 6, max 13, moderate - severe | severe TBI | MD catheter in macrospopical ly normal brain | 25 | lactate, pyruvate, glucose | None | Yes
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Age, TBI</th>
<th>Location</th>
<th>Injury Site</th>
<th>Outcome Measures</th>
<th>Results</th>
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<tbody>
<tr>
<td>Sala et al.</td>
<td>2013</td>
<td>Switzerland</td>
<td>Prospective Observational</td>
<td>24</td>
<td>Median 5, Max 8</td>
<td>Severe TBI</td>
<td>Normal brain parenchyma 21/24, pericontusiona 13/24</td>
<td>None, lactate, pyruvate, glucose, glutamate</td>
<td>Yes</td>
</tr>
<tr>
<td>Sarrafzadeh et al.</td>
<td>2009</td>
<td>Germany</td>
<td>Prospective Observational</td>
<td>41</td>
<td>&lt;9</td>
<td>Severe TBI</td>
<td>Right Frontal</td>
<td>None, lactate, glucose, pyruvate, glutamate, glycerol</td>
<td>ICP, CPP, PbtO2</td>
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<tr>
<td>Singla et al.</td>
<td>2016</td>
<td>India</td>
<td>Prospective Observational</td>
<td>41</td>
<td>&lt;9</td>
<td>Severe TBI</td>
<td>Injured side in parenchyma 45</td>
<td>None, lactate, glucose, pyruvate, glutamate, glycerol</td>
<td>ICP, CPP (CPP cutoff 70)</td>
</tr>
<tr>
<td>Stein et al.</td>
<td>2012</td>
<td>United States</td>
<td>Prospective Observational</td>
<td>89</td>
<td>Between 3 - 12</td>
<td>Moderate - Severe</td>
<td>Right Frontal</td>
<td>25, glucose, lactate, glutamate, pyruvate, glycerol</td>
<td>ICP, CPP</td>
</tr>
<tr>
<td>Svedung Wettervik et al.</td>
<td>2020</td>
<td>Sweden</td>
<td>Retrospective Cross-sectional</td>
<td>115</td>
<td>&lt;9, Motor &lt;6</td>
<td>Severe TBI</td>
<td>Right Frontal</td>
<td>25, glucose, lactate, pyruvate</td>
<td>Arterial lactate conc, ICP; CPP, PRx</td>
</tr>
<tr>
<td>Svedung Wettervik et al.</td>
<td>2019</td>
<td>Sweden</td>
<td>Prospective Observational</td>
<td>120</td>
<td>&lt;9, Motor &lt;6</td>
<td>Severe TBI</td>
<td>Right Frontal</td>
<td>None, glucose, lactate, pyruvate</td>
<td>Arterial glucose conc, ICP, PRX</td>
</tr>
<tr>
<td>Svedung Wettervik et al.</td>
<td>2020</td>
<td>Sweden</td>
<td>Retrospective Cross-sectional</td>
<td>115</td>
<td>&lt;9, Motor &lt;6</td>
<td>Severe TBI</td>
<td>Right Frontal</td>
<td>25, glucose, lactate, pyruvate, glutamate</td>
<td>Arterial oxygenation</td>
</tr>
<tr>
<td>Timofeev et al.</td>
<td>2021</td>
<td>United Kingdom</td>
<td>Prospective Observational</td>
<td>223</td>
<td>Between 3 - 15</td>
<td>Severe TBI</td>
<td>Mostly right frontal, on CT perilesional</td>
<td>25, glucose, lactate, glutamate</td>
<td>ICP; CPP, PRx, PbtO2</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>Duration</td>
<td>TBI Severity</td>
<td>Methodology</td>
<td>Metabolites</td>
<td>Outcome</td>
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<tr>
<td>Timofeev et al.</td>
<td>2013</td>
<td>United Kingdom</td>
<td>Prospective Observation</td>
<td>56 days</td>
<td>Severe TBI</td>
<td>2665 hours, right frontal, pyruvate, glycerol</td>
<td>Glucose, lactate, glutamate, pyruvate, glycerol, PbtO2 (&lt;1.5kPa, 11mmHg), pHbt (&lt;7.15)</td>
<td>Yes</td>
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<tr>
<td>Valadka et al.</td>
<td>198</td>
<td>United States</td>
<td>Prospective Observation</td>
<td>5 days</td>
<td>Severe TBI</td>
<td>Normal brain parenchyma, None</td>
<td>Glucose, lactate, glutamate, pyruvate, glycerol, PbtO2, ICP (all refractory ICP)</td>
<td>Yes</td>
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<tr>
<td>Vespa et al.</td>
<td>2003</td>
<td>United States</td>
<td>Prospective Observation</td>
<td>30 days</td>
<td>&lt;9 or &lt;12 with positive CT</td>
<td>Severe TBI, 2708 hours, normal brain parenchyma, None</td>
<td>Glucose, lactate, glutamate, pyruvate, glycerol, ICP, PET, CPP</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Vespa et al.</td>
<td>2007</td>
<td>United States</td>
<td>Prospective Observation</td>
<td>21 days</td>
<td>&lt;9 or &lt;12 with positive CT</td>
<td>Severe TBI, 2198 hours, normal brain parenchyma and perilesional (2 locations)</td>
<td>Glutamate, pyruvate, lactate, glucose, ICP, CPP, PbtO2</td>
<td>No</td>
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<tr>
<td>Vespa et al.</td>
<td>2005</td>
<td>United States</td>
<td>Prospective Observation</td>
<td>19 days</td>
<td>&lt;9 or &lt;12 with positive CT</td>
<td>Severe TBI, 2614 hours, adjacent to ventriculostomy (R frontal)</td>
<td>Glucose, lactate, glutamate, pyruvate, glycerol, PET (CMRgluc, CMRO2, CBF, OEF, OGR, ICP, PbtO2, CPP)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Vespa et al.</td>
<td>1998</td>
<td>United States</td>
<td>Prospective Observation</td>
<td>17 days</td>
<td>&lt;9</td>
<td>Severe TBI, 772 hours, right frontal</td>
<td>Glutamate, aspartate, glycine, ICP, CPP, EEG</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yokorobi et al.</td>
<td>2011</td>
<td>Japan</td>
<td>Prospective Observation</td>
<td>30 days</td>
<td>&lt;9</td>
<td>Severe TBI, 1560 + 1947 hours, penumbra</td>
<td>Glucose, lactate, glutamate, pyruvate, glycerol, ICP, CPP</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Sample Size</td>
<td>Severity</td>
<td>Tissue</td>
<td>Biomarkers</td>
<td>Monitoring Parameters</td>
<td>Outcome</td>
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<tr>
<td>Yokorobi et al.</td>
<td>2011</td>
<td>Japan</td>
<td>25</td>
<td>&lt;9</td>
<td>severe</td>
<td>TBI</td>
<td>PRx, ICP, CPP</td>
<td>No</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>penumbra</td>
<td></td>
<td>glucose, lactate, glutamate, pyruvate, glycerol</td>
<td></td>
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</tr>
</tbody>
</table>

**Legend:** PET: positron emission tomography, ICP: intracranial pressure, PbtO2: brain tissue oxygen tension, CPP: cerebral perfusion pressure, PRx: pulsatility index, CBF: cerebral blood flow, CMRgluc: cerebral metabolic rate of glucose, CMRO2: cerebral metabolic rate of oxygen, OEF: oxygen extraction fraction, OGR: oxygen glucose ratio, EEG: electroencephalography, SD: spreading depolarization