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REPORT NUMBER 21

# CEREBRAL MICRODIALYSIS AS A TOOL FOR NEUROMONITORING FOLLOWING TRAUMATIC BRAIN INJURY

**Report available at**

**www.mcgill.ca/tau/**

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*Invitation.*

*This document was developed to assist decision-making in the McGill University Health Centre.  All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.*

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## EXECUTIVE SUMMARY

**Background** Cerebral microdialysis (CMD) is a method for sampling biochemical markers of secondary brain damage from cerebral interstitial tissue fluid. This technique has only recently begun to be used for monitoring human brain chemistry in neurointensive care units (NICUs).

**Objective** The purpose of this report is to summarize current literature on the efficacy and safety of this method among traumatic brain injury (TBI) patients.

**Cost** The estimated cost of CMD is an initial investment of $150,000 for purchase of the bedside analyzer. Subsequently there will be an annual cost of $50,000 per annum for purchase of materials (catheters, reagents, vials etc). It will be used on approximately 60 patients annually.

**Methods** A literature search was carried out using PUBMED, the Cochrane database of systematic reviews and INAHTA. Inclusion criteria were: English language, evaluation of at least one of the four most common biochemical markers - glucose, lactate, pyruvate and glutamate, evaluation of the association between CMD measures and either clinical outcomes or markers of cerebral ischemia, CMD used in the NICU (not during surgery), CMD not being used to evaluate a therapeutic intervention, adult patients and minimum sample size of 10. Given that no article reported sensitivity and specificity of CMD it was not possible to perform a quantitative summary of its performance. Therefore a qualitative summary was performed.

**Results** 19 articles satisfied the inclusion criteria, of which 13 studies had a sample size less than 50. The most commonly evaluated clinical outcomes were: death and clinical status using the Glasgow outcome scale following discharge from hospital. Most studies evaluated the association between CMD results and simultaneously measured markers of cerebral ischemia such as hypoxia, intracranial hypertension, systemic hypotension, global oxygen delivery or cerebral blood flow. Though several studies reported observing decreased glucose, increased lactate, increased lactate/pyruvate ratio and increased glutamate in association with an adverse event as measured by either clinical

outcomes or markers of cerebral ischemia, these results was not consistent across studies. One study reported that this pattern was noticed in the absence of any adverse event in a small group of patients.

**Conclusions** There is some evidence in these studies that cerebral metabolic abnormalities revealed by CMD may correlate with evidence of certain potential causes of cerebral ischemia and with adverse clinical outcomes. The available literature does not provide sufficient proof of the efficacy of CMD as a predictor of clinical outcomes to justify its introduction as a clinical monitoring procedure in TBI patients. It has yet to be evaluated using established methods for evaluation of a diagnostic modality. Thus, while CMD may be a procedure with some research promise, it is not yet a clinically applicable tool.

<u>**Recommendation.**</u>  **It is recommended that the MUHC not purchase this equipment at this time. Any application of this technology at the MUHC should be considered to be in the category of research, and supported by research funds.**

## GLOSSARY

**CPP:**        Cerebral perfusion pressure
**CBF:**        Cerebral blood flow
**CBV:**        Cerebral blood volume
**CMA 600:**    Bed-side microdialysis analyzer manufactured by CMA Microdialysis
**EAA:**        Excitatory Amino Acids
**GCS:**        Glasgow Coma Scale
**GOS:**        Glasgow Outcome Scale
**HPLC:**       High Performance Liquid Chromatography
**ICP:**        Intracranial pressure
**L/P ratio:**  Lactate/Pyruvate ratio
**L/G ratio:**  Lactate/Glutamate ratio
**MAP:**        Mean arterial pressure
**NICU:**       Neurointensive Care Unit
**OEF:**        Oxygen Extraction Fraction
**PET :**       Positron Emission Tomography
**PtiO$_2$:**   Brain tissue oxygen tension
**SAH:**        Sub-arachnoid hemorrhage
**SjvO$_2$:**   Jugular venous oxygen saturation:
**TBI:**        Traumatic Brain Injury
**YSI 2700**:   Bioprocess Monitor manufactured by YSI Life Sciences Inc

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## INTRODUCTION

An important aspect of the treatment of patients with Traumatic Brain Injury (TBI) is the prevention of secondary insults, particularly cerebral ischemia, which could adversely affect outcome. Based on neuroimaging studies, risk of ischemic injury in these patients can be as high as 31% during the first 6 hours post-injury and 39% during the initial hospital admission[1]. The mechanism of secondary damage is triggered by reduced oxygen delivery leading to failing energy metabolism, excess calcium overload, enhanced production of oxygen free radicals, neurotoxic effects of excitatory amino acids and inflammatory cell recruitment[2;3].

Neuromonitoring using cerebral microdialysis (CMD) has been proposed as a method for early detection of changes in biochemical markers that may help predict the onset of secondary damage and guide management of these patients. The advantage of CMD over neuroimaging methods such as positron emission tomography (PET) is that it allows real-time assessment of these markers[1]. Its advantage over other monitoring techniques such as measurement of jugular venous oxygen saturation ($SjvO_2$) and brain tissue oxygen saturation ($PtiO_2$) is that it measures metabolism at the cellular rather than the global level[4].

It is only over the last three decades that CMD has been used for studying human brain tissue. The only commercially available bedside CMD analyzer (CMA 600, Sweden) received approval of the Food and Drug Administration (FDA) in the United States as recently as 2002. A consensus document recognizing the increased used of microdialysis [2] has also appeared within the last 3 years with the aim of defining various issues in CMD use such as catheter location and unreliable values of biomarkers.

Cerebral microdialysis has also been used for monitoring during neurosurgical procedures, and for monitoring patients with sub-arachnoid hemorrhage, stroke

and epilepsy. It has also been used to evaluate the impact of therapeutic interventions. In this report we focus on articles evaluating the association between CMD measures and clinical outcomes, and the association between CMD measures and the presence of other markers of cerebral ischemia (eg. hypoxia) in adult patients with TBI. In particular, we focus on the use of CMD for sampling glucose, lactate, pyruvate and glutamate.

## The microdialysis technique

The CMD catheter measures the concentration of chemicals in the extracellular space of the brain by mimicking the action of a blood capillary. It is a very fine tube (diameter ~ 0.6mm, length ~ 10mm) lined with polyamide dialysis membrane at its tip[2;3]. It is inserted into the brain via a burr hole and tunneled under the scalp, or inserted via a bolt-fixation device[3]. CMD monitoring is typically used in patients in whom intracranial pressure is being monitored and the CMD catheter may be inserted into the same burr hole used for the intracranial pressure monitor. Therefore it does not involve any additional invasive procedures besides those that are standard for monitoring TBI patients. The location of the catheter is usually verified using a CT scan.

The CMD catheter is perfused with a physiologic solution at very low flow rates (0.1-2$\mu$L/minute). This solution equilibrates with the surrounding interstitial tissue allowing diffusion of chemicals over the dialysis membrane, without the need to remove any fluid from the brain. Molecules below the cut-off limit of the membrane (~20,000 daltons) can diffuse across the membrane. The collected dialysate reflects the composition of the surrounding interstitial fluid[1]. However, the recovery rate is not 100% and is determined by a number of factors as explained below. The perfusion fluid is collected in vials, which may be changed between 10 to 60 minutes. The vials, with volumes as low as 6$\mu$L, may be analyzed either online by a bedside analyzer or off-line in the laboratory. The latter method may require freezing and thawing of samples.

Hutchinson et al, found that variations in catheter membrane length and flow rate had an important impact on the CMD measurements [5]. It should be noted that these results are based on very small numbers of patients (<10). An improvement in the recovery rate of the order of 102-338% was observed for a catheter length of 30mm compared to 10mm. The observed differences were attributed not only to the length of the catheter membrane in contact with the tissue, but also the heterogeneity of the brain tissue along this length. They found that a slower flow rate of 0.3$\mu$L/minute resulted in a relative recovery of 65-72% microdialysate concentration compared to the extracellular concentration. When the flow rate was increased to 1$\mu$L/minute the relative recovery dropped to 21-34%.

Microdialysis measurements reflect the local tissue chemistry of the region where the catheter is placed. Therefore, appropriate catheter location is crucial in order for CMD measurements to accurately predict global outcomes. Several catheters may be inserted into the brain simultaneously to study different regions[3]. A recent consensus agreement recommended that in TBI patients with diffuse injury one catheter may be placed in the right frontal region, while in patients with focal mass lesions two catheters should be used – one in the pericontusional tissue and one in normal tissue[2]. There is evidence that catheters placed in injured and normal tissue could give very different results[6,7].

The CMA600 is the only commercially available bedside analyzer[8,9]. It was approved for use in the United States in 2002.  Reagents are currently available for sampling glucose, lactate, pyrvuate, glutamate, glycerol and urea. Samples are analyzed using spectrophotometry.  Up to 3 patients with 3 catheters each can be analyzed at the same time. A strong correlation has been demonstrated between high performance liquid chromatography, the gold-standard, and CMA 600 for sampling glutamate [5].

## Biochemical markers

The value of CMD for neurochemical monitoring is directly dependent on the availability of biochemical markers that reliably reflect the phenomenon that one wishes to monitor. There are several chemical substances that can be monitored by CMD including markers of energy metabolic disturbances (eg. glucose, lactate, pyruvate, xanthine), excitotoxicity (eg. glutamate, aspartate), tissue damage and inflammation (ex. glycerol, potassium), and exogenous substances (eg. administered drugs)[3]. Monitoring multiple markers has been found to be more meaningful than any one alone [10]. In this report we focus on the four most common markers – glucose, lactate, pyruvate and glutamate.

*Glucose metabolism*

Glucose, lactate and pyruvate levels can be used to study glucose delivery and utilization, and the extent of anaerobic glycolysis [10].

Glucose: The CMD glucose concentration reflects the balance between capillary delivery and cellular uptake[6]. Low levels would indicate greater demand than supply and are characteristic of ischemia.

Lactate, pyruvate and Lactate/Pyruvate ratio: During ischemia pyruvate is metabolized anaerobically into lactate. Therefore it is hypothesized that ischemia is accompanied by decreasing pyruvate levels and increasing lactate levels[3] and an increase in the lactate/pyruvate ratio. Another reason for high lactate levels could be glutamate induced glycolysis.[11] [3].

Monitoring of lactate alone may be less informative as interstitial lactate levels do not necessarily rise during complete ischemia and because the production of lactate depends on glucose which may fall during complete ischemia[3]. The lactate/pyruvate ratio is considered a more specific marker for cerebral ischemia than lactate alone as it removes the effect of the recovery rate [3;12].

In summary, the following pattern of biochemical markers has been interpreted as evidence that the sampled tissue is approaching energy failure due to lack of oxygen/glucose[10]:

|  | Glucose | Lactate | Pyruvate | L/P ratio | L/G ratio |
|---|---|---|---|---|---|
| Ischemia | ↓↓ | ↑ | ↓ | ↑↑ | ↑↑ |

↓ (↑) and ↓↓ (↑↑) indicates a moderate or marked decrease (increase), respectively

*Excitotoxicity*

Excitotoxicity, or interstitial accumulation of excitatory amino acids such as glutamate, is also hypothesized to be a marker of secondary insults such as ischemia, though there has been some debate over this [10].

**Safety of CMD**

A possible side-effect of microdialysis is an adverse tissue reaction at the site of the catheter. When implantation lasts a long time it could result in glycolysis around the probe resulting in a diffusion barrier. None of the studies included in this review reported these problems. Another problem is that it may take several hours following insertion for CMD measures to stabilize making it difficult to say whether increase in marker levels is artifactual or due to ischemia. It has been noted that an artifactual increase in lactate is usually accompanied by one in glucose[13].

**Estimated cost of CMD at the MUHC**

Annually about 100 patients are treated for brain injuries at the MUHC. Microdialysis may be used for neuromonitoring in an estimated 60% of these patients who will qualify for intracranial pressure monitoring. The remaining 40% are not monitored because they improve very quickly, are too seriously injured or need emergency surgery to remove a large hematoma and do not need a monitoring device afterwards. The estimated cost of CMD is an initial investment of $150,000 for purchase of the bedside analyzer. The lifetime of the analyzer is

unknown, but if a 10-year longevity were assumed, amortization would be at the rate of $15,000 per year  Subsequently there would be an annual cost of $50,000 per annum for purchase of materials (catheters, reagents, vials etc). Thus, excluding any costs for additional nursing time needed to collect the microdialysis samples and transfer them to the analyzer, the annual cost of monitoring 60 patients per year would be approximately $ 65,000. No special training is needed.

## Measurement of Outcomes

In the studies reviewed in this report, relationships were most frequently evaluated between  CMD measures and the following (cut-off values are only approximate and vary across studies):

- GOS: Glasgow outcome scale. Measures neurological deterioration. 1-2 Death or severe disability, 3-4 moderate disability, 5+ good outcome.
- $PtiO_2$: Brain tissue oxygenation. Regional measure of oxygen delivery. Values <10mmHg indicate hypoxia.
- ICP: Intracranial pressure. Values > 20mmHg indicate intracranial hypertension
- CPP: Cerebral perfusion pressure. Values < 70mmHg indicate systemic hypotension.
- $SjvO_2$: Jugular venous oxygen saturation. Global measure of oxygen delivery. Values < 50% indicative of hypoxia.
- CBF: Cerebral blood flow. Values < than $20ml100g^{-1}min^{-1}$ indicative of ischemia.
- Hyperglycemia: Blood glucose concentration of < 15mmol/l;>270mg/dl associated with worse neurological outcome.

## METHODS

Articles were identified from a search of PUBMED, the Cochrane database of systematic reviews and the INAHTA database. The keywords used are given in

Appendix A. Inclusion criteria were English language, evaluation of at least one of the four most common biochemical markers measured using CMD - glucose, lactate, pyruvate and glutamate, evaluation of the association between CMD measures and either clinical outcomes or markers of cerebral ischemia, CMD used in NICU (not during surgery), CMD not being used to evaluate a therapeutic intervention, adult patients and minimum sample size of 10. We chose to limit our report to adult patients as CMD would only be used for neuromonitoring of adult patients at the MUHC. Further, it is not clear that results of pediatric studies can be extended to adults. Bibliographies of articles satisfying the inclusion criteria were further searched for relevant articles.

Information extracted from individual articles included: sample size, microdialysis settings, biochemical markers, outcome variables and adverse effects. The methodological quality of individual studies was evaluated using criteria, described by the Cochrane Diagnostic Methods Group (http://www.cochrane.org/docs/sadtdoc1.htm) and the STARD initiative[14], that are summarized in the table below (interpretations when applying these criteria to CMD studies are given in brackets):

| 1 | Was at least one valid reference test used? (valid reference = established measure of secondary insult or neurological deficit) |
|---|---|
| 2 | Was the reference test applied in a standardized manner? (standardized manner = standard cut-off on reference test) |
| 3 | Was each patient submitted to at least one valid reference test? |
| 4 | Was the rationale and definition of a cut-off given for the CMD measures? (Was the magnitude of a clinically meaningful cut-off or a clinical meaningful change specified for the CMD measures?) |
| 5 | Were the interpretations of the index test and reference test performed independently of each other? (Were CMD measurements and outcome measurements obtained independently of each other?) |
| 6 | Was the choice of patients who were assessed by the reference test independent of the results of the index test? |

7    Was the study design prospective? (Did CMD measurement precede outcome measurement?)

8    Was a description included regarding missing data? (Was percentage of missing/eliminated data reported?)

9    Were data adequately presented in enough detail to calculate test characteristics such as sensitivity and specificity?

## RESULTS

The results of our literature search are summarized in Figure 1. A total of 140 articles were identified using our search strategy. The most common reason for exclusion was that the study was conducted in pediatric patients. All articles were identified from PUBMED. No systematic review or technology assessment reports were found that satisfied our inclusion criteria. A total of 19 articles satisfied our inclusion criteria – 4 on markers of glucose metabolism, 4 on markers of excitotoxicity and 11 on both. They were published between 1996-2005. Sample sizes ranged from 11 to 126, with 13 studies having a sample size less than 50. The studies are summarized in Appendix B.

## Methodological quality

The methodological quality of the different studies is summarized in Table 1. No study provided information on the sensitivity or specificity of CMD. Only 4 studies specified a clinically meaningful cut-off or a clinically meaningful change for the CMD markers[12;13;15;16]. Most studies reported the association between different CMD measures or between CMD measures and simultaneously measured predictors of ischemia. In only one study evaluating the relation between CMD measures and another marker (hypoxia), the marker was measured *after* CMD occurring during hospitalization[17]. Seven studies evaluated the predictive value of CMD measures for clinical outcomes (death or performance on the GOS scale during follow-up) [18].

Statistical analyses were inadequate in most papers as they usually ignored correlation between multiple measurements on an individual patient and variation in number of hours each patient was followed for. None of the studies measured the reproducibility of CMD. Studies involved a mix of patients with varying severity of TBI.

**Summary of CMD characteristics in the different studies**

Details of CMD catheter positioning, biochemical markers sampled and method of analysis in each study are given in Appendix B. In most studies the catheter was placed in the right frontal cortex in grossly normal appearing tissue. Nine studies (~50%) used the CMA 600 bedside analyzer. These studies were all published in the year 2000 and later and represent 80% of the studies reviewed from that time period. Most studies using the CMA 600 analyzer reported using a membrane length of 10mm and Ringer's solution as perfusion fluid at a flow rate of 0.3µL/min (data not presented). Study samples were taken once hourly. From the pre-2000 period, most studies included in our review used HPLC for analysis. These studies usually reported using saline as the perfusion fluid at a flow rate of 2µL/min (data not presented). Samples were taken every 30 minutes. Only one study reported using a specially constructed rapid sampling CMD system that collected samples every 30s[16].

**Summary of evaluation of CMD measures for predicting secondary insults**

In this section we summarize results on the association of CMD with each outcome variable. A more detailed summary of each study is given in Appendix B. A summary of the association between CMD measures and adverse events is given in Table 2. Many studies did not explicitly report whether there was a lack of association between CMD measures and outcomes. Therefore, when they did not report any association we concluded there was none. Associations presented may include those that were not statistically significant as some studies did not give sufficient details.

*Poor outcome on GOS/Death or disability during follow-up*[9;13;15;18-21]

Three out of 4 studies found lower glucose and higher glutamate values to be associated with this outcome.

*Hypoxia (PtiO$_2$)* [12;15;17;18;22-25].

> Lower glucose levels were most consistently associated with impending or present hypoxia. High lactate, glutamate and L/P ratios were also associated with hypoxia but not consistently in all studies.

*Intracranial hypertension (ICP)* [19;21;26]

> There was no consistent relation between ICP and CMD measures.

*Systemic hypotension (CPP)* [15;26;27]

> There was no consistent relation between CPP and CMD measures[21].

*Jugular venous oxygen saturation (SjvO$_2$)* [15;22]

> There was no consistent relation between SjvO$_2$ and CMD measures

*Cerebral blood flow (CBF)* [15;23;28]

> Low CBF was associated with low glucose, high lactate and high glutamate values.

*Hypoglycolysis*

> In a study by Goodman et al.[13] increased lactate and decreased glucose were noticed in 10 out of 126 patients. The authors report that unlike the transient patterns they noticed during ischemia these patterns lasted several hours or days.

*Other outcomes*

> Hyperglycemia was the only adverse outcome associated with higher glucose values[29]. An increase in the number of depolarization events was associated with lower glucose[16]. Two studies used a composite outcome including multiple measures described above[13;30]. From these studies it appeared that an adverse event was associated with low glucose, high lactate and high glutamate values.

**<u>Adverse effects of microdialysis</u>**

None of the studies reviewed reported any adverse effects.

## DISCUSSION

There has been increasing interest in the use of CMD as a diagnostic tool for monitoring patients with TBI. It has been suggested that microdialysis may be used to study the mechanisms of ischemic damage, as represented by metabolic fluctuations, and may thus help reduce the occurrence of ischemia and other potentially preventable secondary insults in these patients. This report summarizes the available literature evaluating the association between common biochemical markers (glucose, lactate, pyruvate, glutamate) measured using CMD and clinical outcomes or other markers of ischemia.

A total of 19 studies satisfied our inclusion criteria. None of the studies reported results in a form that allowed us to estimate the sensitivity and specificity of CMD, statistics that are recommended for evaluating a diagnostic modality[14]. The most commonly studied clinical outcome was death or GOS score, a measure of neurological deficit. Several studies reported the association between CMD results and the presence of other factors likely to cause cerebral ischemia. In general a pattern of low glucose, high lactate, high glutamate and high L/P values appeared to be associated with death/severe disability, local and global hypoxia and low cerebral blood flow. However, this pattern was not consistent across studies and outcomes. Moreover, there were instances when this pattern was observed in the absence of an adverse event[13].

Most studies did not specify what they considered a clinically meaningful cut-off to determine low or high values on each biochemical marker or change in the marker. No study reported the validity of the other markers to which CMD was being compared. If the marker being used as a reference is itself not a good predictor of ischemia, comparing CMD to it does not increase our knowledge of the latter. Most studies had small sample sizes and did not use appropriate statistical methods that take into account the variable number of observations per

patient, and adjust for the correlation between multiple measurements on each patient.

Research into the evaluation of CMD for routine use in the NICU is still in its infancy. In order to allow for evaluation of CMD using accepted standards future studies would need to define clinically meaningful cut-offs for low/high values and for change on each marker so that their sensitivity and specificity can be defined. One of the difficulties in defining such a cut-off value has been the variability in recovery rate and the great variability in these markers across patients[21]. The introduction of the CMA 600 should address the former problem. The sensitivity and specificity of the marker to which CMD is being compared should be noted. The interpretation of a low or high association between CMD and another marker would depend on the validity of that marker for cerebral ischemia. It would also be important to evaluate whether abnormal values on CMD can be detected in a clinical setting in which corrective measures are possible, since it is clearly not productive to detect ischemia in the absence of any means for its correction. Finally, appropriate statistical methods should be used that take into account the dependence between multiple measurements on each individual. Given the great variability in CMD measures across patients it is possible that combining information across patients in one sample may have resulted in an exaggeration of the linear correlation with outcomes due to the increase in range of the CMD measure. Some studies have attempted to address this problem by calculating a separate correlation coefficient for each patient and reporting the average across patients. This is also inappropriate as patients would receive the same weight whether they contributed very few or many observations.

Recent review articles on CMD suggest that while it is a promising tool for neuromonitoring further research is needed before it can be used routinely. An article by one of the pioneers in the development of this technology recently concluded that microdialysis "…**has the potential of becoming an established part of multimodality neuro-ICU monitoring, contributing unique**

**information about the acute brain injury process. However, in order to reach this stage, several issues related to quantification and bedside presentation of CMD data, implantation strategies, and quality assurance need to be resolved"**[10]. A recent consensus document concluded tentatively that **"Microdialysis may be useful in severe cases of SAH and TBI in which monitoring of intracranial pressure and cerebral perfusion pressure is required"**[2]. A systematic review of microdialysis for neuromonitoring among patients with SAH concluded that there wasn't sufficient evidence in its favour to recommend it for routine use in the NICU[31].

## CONCLUSIONS

There is some evidence in these studies that cerebral metabolic abnormalities revealed by CMD may correlate with evidence of certain potential causes of cerebral ischemia and with adverse clinical outcomes. The available literature does not provide sufficient proof of the efficacy of CMD as a predictor of clinical outcomes to justify its introduction as a clinical monitoring procedure in TBI patients. It has yet to be evaluated using established methods for evaluation of a diagnostic modality. Thus, while CMD may be a procedure with some research promise, it is not yet a clinically applicable tool.

**RECOMMENDATION.  It is recommended that the MUHC not purchase this equipment at this time. Any application of this technology at the MUHC should be considered to be in the category of research, and supported by research funds.**

## FIGURE 1: RESULTS OF LITERATURE SEARCH

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            ┌─────────────────────┐
            │  Articles identified │
            │   using PUBMED       │
            │   search:  140       │
            └──────────┬──────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  Not published       │
                       │             │  in English: 3       │
                       │             └─────────────────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  Pediatric study: 67 │
                       │             └─────────────────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  Sample size < 10: 15│
                       │             └─────────────────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  CMD used as outcome │
                       │             │  in intervention     │
                       │             │  study: 22           │
                       │             └─────────────────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  CMD use during      │
                       │             │  surgery: 1          │
                       │             └─────────────────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  CMD biochemical     │
                       │             │  markers others than │
                       │             │  those identified: 11│
                       │             └─────────────────────┘
                       │
                       │──────────►  ┌─────────────────────┐
                       │             │  No outcomes         │
                       │             │  studied: 2          │
                       │             └─────────────────────┘
                       │
                       ▼
            ┌─────────────────────┐
            │ Articles included in │
            │   report: 19         │
            └─────────────────────┘
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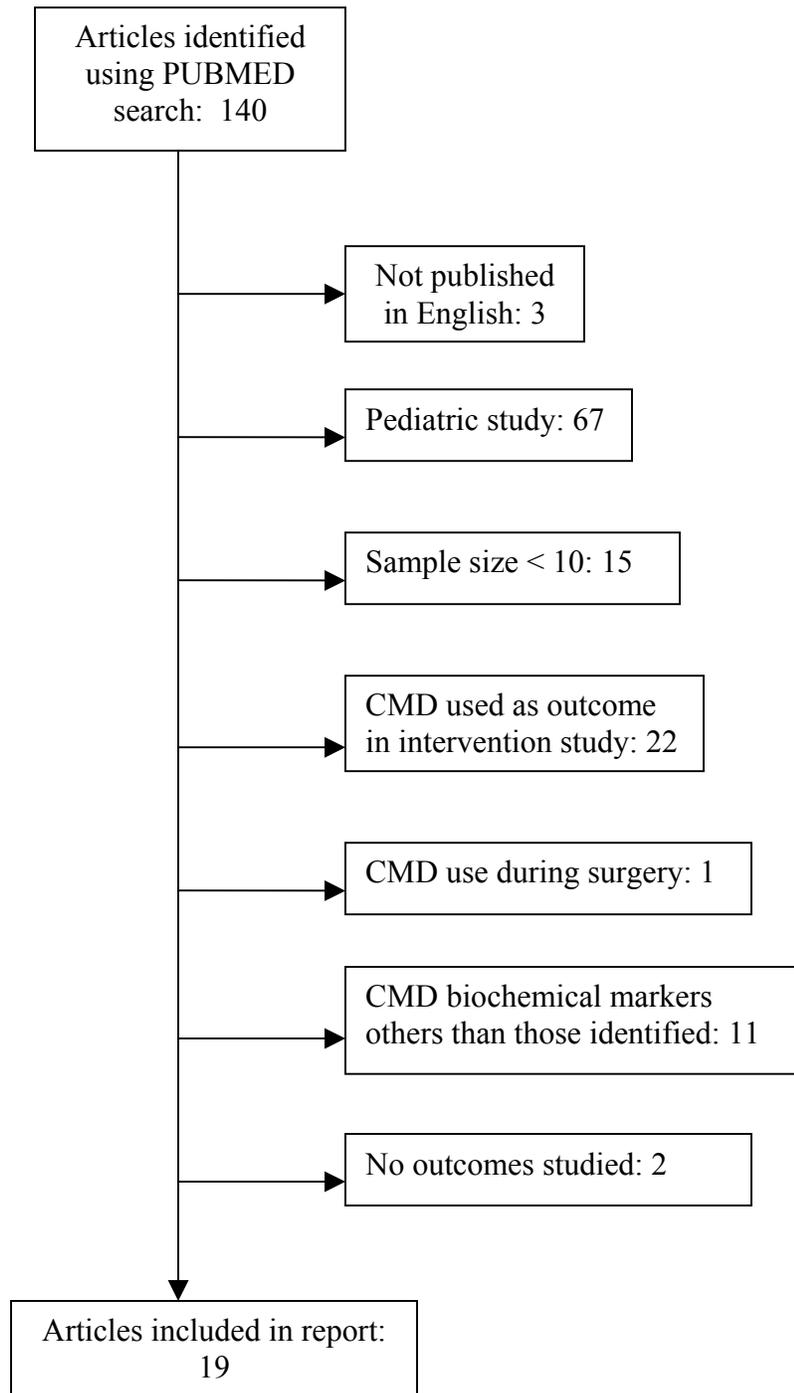
## APPENDIX A: KEYWORDS USED IN LITERATURE SEARCH

Articles were identified in PUBMED using two separate strategies – regular keywords and MeSH (Medical Subject Headings) keywords.

**Regular keyword search (Limit=Human)**:

(microdialysis OR neuromonitoring)

AND

(brain OR cerebral OR head)

AND

(trauma OR injury OR injured)

AND

(glucose OR lactate OR pyruvate OR glutamate)


**MeSH keyword search**:

"Microdialysis"[MeSH]

AND

(((("brain"[MeSH Terms] OR brain[Text Word]) OR (("brain"[TIAB] NOT Medline[SB]) OR "brain"[MeSH Terms] OR cerebral[Text Word]) OR ("head"[MeSH Terms] OR head[Text Word]))

AND

(("injuries"[Subheading] OR ("wounds and injuries"[TIAB] NOT Medline[SB]) OR "wounds and injuries"[MeSH Terms] OR trauma[Text Word]) OR (("wounds and injuries"[TIAB] NOT Medline[SB]) OR "wounds and injuries"[MeSH Terms] OR injury[Text Word]))) AND "humans"[MeSH Terms]


Note: The strategy using MeSH did not make any mention of the measurements taken using microdialysis.

## APPENDIX B:  SUMMARY OF STUDIES

**1. Goodman et al (1996)**[30]
*Sample size:* 34
*CMD variables:*
> *Catheter location:* Grossly normal appearing cortex
> *Biochemical markers:* Lactate, Pyruvate, Glutamate, Other amino acids
> *Analysis:* HPLC

*Other markers:* Pathophysiological event: ICP>25mmHg or $SjvO_2$<50% for 10+ minutes
*Statistical methods:*  Not mentioned
*Results:*
- 78% of lactate elevations accompanied a pathophysiological event
- 87.5% of pathophysiological events associated with lactate elevation
- glutamate and other amino acids also "elevated" during pathophysiological events

*Comments:*
- cannot separate relation with ICP and $SjvO_2$
- do not say whether results were statistically significant


**2. Zauner (1996)**[28]
*Sample size:* 25
*CMD variables:*
> *Catheter location:* Damaged, but viable tissue
> *Biochemical markers:* Glutamate
> *Analysis:* HPLC

*Other markers:* CBF (regional and hemispheric)
*Statistical methods:* Correlation between CBF and glutamate measured during 3-6 hour period closest to CBF measurement
*Results:*
- High correlation (0.895) between glutamate and regional CBF, and moderate correlation between glutamate and hemispheric CBF (0.632)
- Non-significant correlation between peak glutamate and either type of CBF
- All patients with CBF < 16ml/100g/min had a high mean glutamate value >20μM/L.

*Comments:*
- CBF measurements taken at admission were used. This means glutamate may have been artificially elevated due to proximity to time of catheter implantation.
- Not clear why a 3-6 hour period chosen for glutamate measurement or if the duration was variable across patients
- Not clear if CBF measured *prior* to glutamate


**3. Zauner (1997)**[18]
*Sample size:* 21
*CMD variables:*
> *Catheter location:* Not given
> *Biochemical markers:* Glucose, Lactate
> *Analysis*: HPLC

*Clinical outcomes:* GOS at 3 or 6 months after injury
*Other markers:* PtiO$_2$
*Statistical methods:* Multiple logistic regression
*Results:*
- 10 patients died or remained vegetative, 6 were discharged with moderate to severe disability and 8 with a good outcome
- Mean glucose concentration decreased with worsening outcome on GOS, while mean lactate concentration increased. These relations were not statistically significant.
- glucose was significantly correlated with PtiO$_2$, which the authors concluded was the best predictor of GOS

*Comments:*
- CMD probe was part of a multiparameter sensor

## 4. Koura (1998)[32]
*Sample size:* 83
*CMD variables:*
   *Catheter location:* Brain cortex
   *Biochemical markers:* Glutamate, Aspartate
   *Analysis*: HPLC
*Clinical Outcomes:* 6-month scores on GOS
*Other markers:* ICP
*Other outcomes:* Effect of lesion type on EAA release pattern
*Statistical methods:*
- Spearman's correlation between EAA levels
- Linear regression between mean dialysate during entire period and 6-month GOS
*Results:*
- "Significant" correlation between glutamate and aspartate
- Significant positive correlation (0.332) between mean glutamate and GOS
- 85% of patients with good outcomes had mean glutamate values < 20μM/L
- 72% of patients with mean glutamate values >20μM/L had an unfavourable outcome
- Patients with contusional lesions had highest overall EAA levels
- Patients with mean glutamate values > 20μM/L were more likely to have elevated ICP (r=0.554)

## 5. Robertson (1998)[22]
*Sample size:* 44
*CMD variables:*
   *Catheter location:* Cerebral cortex
   *Biochemical markers:* Lactate, Glucose
   *Analysis*: YSI 2700
*Clinical Outcomes:* None
*Other markers:* Cerebral oxygenation (regional measured by PtiO$_2$ and global by SjvO$_2$)
*Statistical methods:* Descriptive statistics
*Results:*
- In the 6 patients who had transient global cerebral ischemia lactate increased and glucose decreased transiently during jugular venous desaturation

- In the 3 patients with local cerebral ischemia lactate increased while glucose decreased

*Comments:*
- Study mainly focuses on relative merits of global and regional measures of cerebral oxygenation. Concludes both are important and that CMD adds information on how lack of oxygenation is affecting metabolism
- Cut-off on $PtiO_2$ not given


**6. Vespa (1998 )**[26]
*Sample size:* 17
*CMD variables:*

    *Catheter location:* Ipsilateral to primary injury in 10 patients;  normal or edematous tissue in remainder

    *Biochemical markers:* Glutamate, Other EAAs (aspartate, glycine, serine)

    *Analysis*: HPLC

*Other markers:* CPP, ICP
*Other outcomes:*
- Neurochemical profile of glutamate
- Impact of other causes of cellular distress (ex. vasospasm, seizures) on glutamate

*Statistical methods:*
- Pearson's correlation of glutamate with CPP and ICP
- t-test comparing glutamate in groups with low vs high CPP

*Results:*
- decreases in CPP were associated with increases in glutamate in 8 patients but not in 2.
- mean glutamate values (across patients) remained higher than the first post-injury day during the 9 days studied.
- Mean glutamate values were significantly higher (30 vs 15.3µM) when CPP was low.
- no correlation between ICP and glutamate
- glutamate values higher on days when patients had seizures or vasospasm

*Comments:*
- use hourly min CPP and max ICP.


**7. Goodman  (1999)**[13]
*Sample size:* 126
*CMD variables:*

    *Catheter location:* Grossly normal appearing cortex

    *Biochemical markers:* Glucose, Lactate

    *Analysis*: YSI 2700

*Clinical outcomes:* Survival
*Other markers:* Severity of ischemia (hypertension, hypotension, hypocapnia, hypoxia, anemia)
*Other outcomes:* Hypoglycolysis (increased lactate and decreased glucose not related to adverse event)
*Statistical methods:*
- Non-parametric repeated measures analysis
- change of glucose or lactate greater than 0.2µM/L was considered significant

*Results:*

- glucose and lactate levels not affected by type of injury (mass lesion vs diffuse) or postresuscitation GCS
- median lactate significantly higher, while glucose significantly lower in patients who died
- increased lactate and faster change in glucose associated with severity of ischemia
- In 10 patients elevation in lactate and decrease in glucose were observed that were not associated with ischemia. These patterns lasted for several hours or days unlike transient patterns seen during ischemia.

*Comments:*
- Two different types of microdialysis probes used
- Adjustment for multiple observations on each patient
- Define a clinically meaningful change for glucose or lactate to be >0.2μmol/mL
- no relation between arterial and dialysate concentrations of glucose and lactate
- lump together different predictors of ischemia


**8. Gopinath (2000)**[20]

*Sample size:* 86

*CMD variables:*

    *Catheter location:* An area in the fronto-temporal region that appeared injured but not necrotic

    *Biochemical markers:* Glutamate, Aspartate

    *Analysis*: HPLC

*Clinical outcomes:* Survival, GOS, GCS,

*Other markers:* Pre-hospital hypoxia/hypotension

*Statistical methods:* Not given

*Results:*
- significantly higher glutamate and aspartate values in patients who died
- higher values also determined by type of injury: gunshot wounds highest
- patients with diffuse injuries had the lowest values
- no association with hypoxia or hypotension


**9. Hutchinson (2000b)**[9]

*Sample size:* 21

*CMD variables:*

    *Catheter location:* Frontal cortex

    *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate

    *Analysis*: CMA 600

*Clnical outcomes:* Died or severely disabled

*Other outcomes:* correlation between CMD measures

*Statistical methods:* Descriptive statistics, correlation

*Results:*
- patients with poor outcome had lower glucose and higher L/P ratio
- patterns of "improvement" and "worsening" seen clearly
- glutamate stabilized with time in all patients but remained high or rose again in those with poor outcomes
- good correlation (0.74) between lactate and pyruvate during "uneventful" monitoring. Moderate correlation between L/P ratio and glutamate (0.48).

*Comments:*
- Do not relate patterns of improvement and worsening to outcomes


## 10. <u>Reinert (2000)</u>[23]
*Sample size:* 85
*CMD variables:*
    *Catheter location:* Right frontal cortex
    *Biochemical markers:* Glutamate, Lactate
    *Analysis*: HPLC (Glutamate), YSI (lactate), IL 943 (potassium)
*Other markers:* CBF (Relation between CMD measures taken ± 1 hour around CBF),
Brain pH, Brain $CO_2$, $PtiO_2$<20mm
*Other Outcomes:* Effect of glutamate on lactate production
*Statistical methods:* Correlation, linear regression, non-parametric tests. A separate correlation was calculated for each patient and then averaged
*Results:*
- Statistically significant correlations of the order of 0.2 were observed between glutamate-lactate, glutamate-brain pH, glutamate-potassium and glutamate-brain $CO_2$
- higher lactate values associated with higher brain tissue $O_2$
- significant inverse relation between CBF and CMD measures: potassium (-0.426), glutamate (-0.92) and lactate (-0.303)

*Comments:*
- All "significant" correlations had a wide range between -1 to 1.


## 11. <u>Hutchinson (2002b)</u>[24]
*Sample size:* 17
*CMD variables:*
    *Catheter location:* Not given
    *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate (Cerebral and
    peripheral values for all markers)
    *Analysis:* CMA 600
*Other markers:* Baseline PET measures (OEF, CBV, CBF, $CMRO_2$), Hypoxia, Hypertension
*Other outcomes:* Feasibility of CMD during PET
*Statistical methods:* Descriptive statistics, correlation
*Results:*
- conclude it is feasible and safe to combine PET and microdialysis
- good correlation between cerebral and peripheral glucose, and between cerebral lactate and cerebral pyruvate
- decreased glucose, increased L/P ratio and decrease in glutamate associated with adverse outcomes such as hypoxia and hypertension
- significant relation between OEF (from PET) and L/P ratio. There was no relation between any other CMD and PET measures

*Comments:*
- do not distinguish between different types of adverse events
- higher glutamate associated with better outcome unlike in other studies
- cutoffs not provided for hypoxia and hypertension

**12. <u>Poon (2002)</u>**[27]

*Sample size:* 23

*CMD variables:*
>  *Catheter location:* Right frontal lobe
>  *Biochemical markers:* Glucose, Lactate, Glutamate, Pyruvate, Glycerol
>  *Analysis:* CMA 600

*Other markers:* CPP

*Statistical methods:* Pearson's correlation

*Results:* CPP positively correlated with glucose and pyruvate, negatively with other biochemical markers. This relation was mainly seen when CPP<65mm

**13. <u>Sarrafzadeh (2002)</u>**[17]

*Sample size:* 24 (2513)

*CMD variables:*
>  *Catheter location:* Non-lesioned frontal white matter
>  *Biochemical markers:* Glucose, Lactate, L/P ratio, Glutamate (all measured
>  during hour before hypoxia)
>  *Analysis:* CMA 600

*Other outcomes:* Hypoxia ($PtiO_2$)

*Statistical methods:* Parametric and Non-parametric ANOVA

*Results:*
- lower Glucose before impending or present hypoxia
- higher Glutamate before present hypoxia
- no change in Lactate or L/P ratio suggesting no anaerob metabolism.

*Comments:* Only study where CMD related to a measure taken at a subsequent time during hospitalization.

**14. <u>Diaz-Parejo (2003)</u>**[29]

*Sample size:* 108

*CMD variables:*
>  *Catheter location:* In more-injured and less-injured tissue
>  *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate, Glycerol
>  *Analysis:* CMA 600

*Other markers:* Hyperglycemia

*Statistical methods:* Paired student's t-test

*Results:*
- Moderate hyperglycemia was observed in 18 patients
- Higher glucose during hyperglycemia episode in both better and worse catheter locations, but no changes in other markers

*Comments:* Multiple CMD catheters in "worse" and "better" tissue

**15. <u>Sarrafzadeh (2003)</u>** [25]

*Sample size:* 41

*CMD variables:*
>  *Catheter location:* Non-lesioned frontal white matter
>  *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate

*Analysis:* CMA 600
*Other markers:* Hypoxia ($PtiO_2$)
*Statistical methods:* ANOVA, non-parametric and chi-square tests
*Results:*
- 280 episodes of impending and 45 episodes of manifest hypoxia observed
- During impending hypoxia, glucose decreased and glutamate was elevated
- During manifest hypoxia glucose was decreased, glutamate was sharply elevated, lactate was elevated, and there were non-statistically significant increases in pyruvate and L/P ratio

*Comments:*
- Exclude first 12 hours of data to ensure stabilization

## 16. Vespa (2003)[15]
*Sample size:* 30
*CMD variables:*
> *Catheter location:* Dorsolateral frontal white matter
> *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate, Urea
> *Analysis:* CMA 600
*Clinical Outcomes:* GOS at 6 months, seizures
*Other markers:* CPP, $SjvO_2$, $PtiO_2$, hypoglycemia, CBF
*Other outcomes:* Time course and nature of CMD glucose, impact of glucose on lactate
*Statistical methods:* Correlation, descriptive statistics, "case-based" regression model
*Results:*
- 72% of low glucose values were not associated with changes on any of the outcome measures (CPP, $SjvO_2$, $PtiO_2$, hypoglycemia and seizures)
- No correlation between glucose and lactate
- "Strong" correlation (0.32) between CBF and glucose
- low glucose associated with poor GOS at follow-up. "Case-based" analysis revealed that lactate/glucose ratio better predictor than lactate or glucose alone

*Comments:*
- article focuses on glucose time course
- threshold for low glucose defined as <0.05mmol/L

## 17. Hlatky (2004)[12]
*Sample size:* 57
*CMD variables:*
> *Catheter location:* Vulnerable brain tissue
> *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate, Glycerol
> *Analysis:* CMA 600
*Other markers:* $PtiO_2$
*Statistical methods:* Multilevel linear modeling
*Results:*
- 7 patients had a total of 10 episodes of hypoxia
- majority of glucose and lactate values during first 12 hours within normal levels
- glucose most consistently related to $PtiO_2$ among CMD measures – fall in $PtiO_2$ associated with lower glucose concentration

- no apparent relation between pyruvate and outcome
- lactate and glutamate both increased with decreasing PtiO$_2$
- Sharp increase in L/P ratio following drop in PtiO$_2$ below 10mm
- conclude that while glucose the earliest predictor of hypoxia, other markers provide an idea of ischemia severity

*Comments:*
- "normal" values of CMD markers provided
- patients may include some minors 15-18 yrs
- PbtO$_2$ was preferred to SjvO$_2$ as a measure of hypoxia due to its sensitivity to local hypoxia.
- statistical methods adjust for multiple measurements on each patient
- arbitrary cut-off values for low PbtO$_2$ may have resulted in some loss of precision. Also PbtO$_2$ values averaged over 1 hour so any changes during that period are not accounted for.
- total number of hours of hypoxia not reported


**18. <u>Nelson (2004)</u>**[21]
*Sample size:* 26
*CMD variables:*
> *Catheter location:* Penumbral tissue and healthy non-penumbral tissue contralateral to the injury
> *Biochemical markers:* Glucose, Lactate, Pyruvate, Glutamate (Penumbral and non-penumbral)
> *Analysis:* CMA 600

*Other markers:* ICP, CPP, GOS
*Statistical methods:* Kohonen Self Organizing Map
*Results:*
- Almost 50% of CMD data excluded for various reasons such as instability of readings soon after insertion of catheter
- CMD values exhibit highly individual patterns
- No clear relation with any outcome

*Comments:*
- Complex statistical analysis. Early CMD results were used for training and prediction of later results.
- Degree of "individuality" unclear. Did patients vary greatly in absolute values of CMD measures and variance over time?


**19. <u>Parkin (2005)</u>**[16]
*Sample size:* 11
*CMD variables:*
> *Catheter location:* Placed during surgery within 1cm of nonviable tissue
> *Biochemical markers:* Glucose, Lactate
> *Analysis:* Custom-built dual online assay system

*Other outcomes:* changes in CMD measures, depolarisation event
*Statistical methods:* Pearson's correlation
*Results:*
- changes classified as transient increase, transient decrease, biphasic change and fluctuation

- "no of events" (i.e. clinically meaningful changes) in glucose and lactate CMD measurements were correlated.
- decrease in glucose levels correlated with increasing number of depolarisation events
***Comments:***
- only paper on rapid sampling CMD involving much more frequent CMD measurements
- provide a value for clinically meaningful change in CMD measures
- not clear if the change in glucose precedes depolarisation event

Table 1: Summary of study quality

| + Yes, - No, ? Not clear | Goodman (1996)[30] | Zauner (1996)[28] | Zauner (1997)[18] | Koura (1998)[19] | Robertson[22] | Vespa (1998)[26] | Goodman (1999)[13] | Gopinath (2000)[20] | Hutchinson (2000b)[9] | Reinert (2000)[23] | Hutchinson (2002)[24] | Poon (2002)[27] | Sarrafzadeh (2002)[17] | Diaz-Parejo (2003)[29] | Sarrafzadeh (2003)[25] | Vespa (2003)[15] | Hlatky (2004)[12] | Nelson (2004)[21] | Parkin (2005)[16] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Was at least one valid reference test used ? | + | + | + | + | + | + | + | + | + | ? | + | + | + | + | + | + | + | + | + |
| 2. Was the reference test applied in a standardized manner? | - | + | + | + | +/? | + | + | +/- | + | +/- | ? | + | + | + | + | + | + | + | + |
| 3. Was each patient submitted to at least one valid reference test? | + | + | + | + | + | + | + | + | + | ? | + | + | + | + | + | + | + | + | + |
| 4. Was the rationale and definition of a cut-off given for the CMD measures? | - | + | - | - | + | - | + | - | - | - | - | - | - | - | - | + | + | - | + |
| 5. Were the interpretations of the index test and reference test performed independently of each other? | + | ? | ? | ? | + | + | + | + | + | + | + | + | + | + | + | +/? | + | + | + |
| 6. Was the choice of patients who were assessed by the reference test independent of the results of the index test? | + | + | + | + | + | + | ? | + | + | ? | + | + | + | + | + | + | + | ? | + |
| 7. Was the study design prospective? | - | - | + | + | - | - | +/- | +/- | + | - | - | - | + | - | - | +/- | - | + | ? |
| 8. Was a description included regarding missing data? | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | + | - |
| 9. Were data adequately presented in enough detail to calculate test characteristics (sensitivity and specificity)? | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - |

Table 2: Summary of results of association between CMD measures and outcomes

| Outcome | Glucose | | Lactate | | Pyruvate | | Glutamate | | L/P ratio | | L/G ratio | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | n | N | n | N | n | N | N | N | n | N | n |
| Poor outcome on GOS/Death or disability | 5 | 3↓ | 5 | 1↑ | 3 | 0 | 5 | 3↑ | 1 | 1↑ | 1 | 1↑ |
| Manifest or impending hypoxia | 7 | 6↓ | 8 | 3↑,1↓ | 5 | 0 | 6 | 1↓,3↑ | 3 | 2↑ | - | - |
| Intracranial hypertension | 2 | 1↓ | 2 | 0 | 2 | 0 | 4 | 1↓,1↑ | 1 | 1↑ | - | - |
| Systemic hypotension | 3 | 1↓ | 3 | 1↑ | 3 | 1↓ | 4 | 2↑ | - | - | - | - |
| Low SjvO$_2$ | 2 | 1↓ | 2 | 1↑ | 1 | 0 | 1 | 0 | - | - | - | - |
| Low CBF | 1 | 1↓ | 2 | 1↑ | 1 | 0 | 3 | 2↑ | | | | |
| Hyperglycemia | 1 | 1↑ | 1 | 0 | 1 | 0 | 1 | 0 | - | - | - | - |
| Depolarization Event | 1 | 1↓ | 1 | 0 | - | - | - | - | - | - | - | - |
| Adverse events[*] | 1 | 1↓ | 2 | 2↑ | 1 | 0 | 1 | 1↑ | | | | |

N: Number of studies evaluating the association
n: Number that found a significant result
↑: High or increasing value of CMD measure
↓: Low or decreasing value of CMD measure
*: Results from Goodman 1996 (16) and Goodman 1999 (13) where association with different types of adverse events could not be distinguished.

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