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Neuroenergetic Response to Prolonged Cerebral Glucose Depletion after Severe Brain Injury and the Role of Lactate

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Abstract

Lactate may represent a supplemental fuel for the brain. We examined cerebral lactate metabolism during prolonged brain glucose depletion (GD) in acute brain injury (ABI) patients monitored with cerebral microdialysis (CMD). Sixty episodes of GD (defined as spontaneous decreases of CMD glucose from normal to low [<1.0 mmol/L] for at least 2 h) were identified among 26 patients. During GD, we found a significant increase of CMD lactate (from 4 ± 2.3 to 5.4 ± 2.9 mmol/L), pyruvate (126.9 ± 65.1 to 172.3 ± 74.1 μmol/L), and lactate/pyruvate ratio (LPR; 27 ± 6 to 35 ± 9; all, $p<0.005$), while brain oxygen and blood lactate remained normal. Dynamics of lactate and glucose supply during GD were further studied by analyzing the relationships between blood and CMD samples. There was a strong correlation between blood and brain lactate when LPR was normal ($r=0.56$; $p<0.0001$), while an inverse correlation ($r=-0.11$; $p=0.04$) was observed at elevated LPR >25. The correlation between blood and brain glucose also decreased from $r=0.62$ to $r=0.45$. These findings in ABI patients suggest increased cerebral lactate delivery in the absence of brain hypoxia when glucose availability is limited and support the concept that lactate acts as alternative fuel.

Key words: brain injury; cerebral metabolism; cerebral microdialysis; glucose; lactate

Introduction

The interaction between neurons and astrocytes plays a central role in coupling energy supply with changes in neuronal activity. Neurons and astrocytes are surrounded by interstitial fluid, which contains glucose and lactate. The glucose pool is supplied by blood-derived glucose, whereas lactate is interchanged between glial cells and neurons.[1] According to the astrocyte–neuron lactate shuttle model, glucose is metabolized glycolytically to lactate in astrocytes, which is then transported to the extracellular fluid (ECF) via specific lactate transporters (monocarboxylate transporters MCT-1 and 4).[2] According to arterial blood lactate levels, additional lactate also can be directly transferred from the systemic circulation to the ECF via MCT-1 expressed on endothelial cells.[3,4] Neurons express MCT-2, which allows influx of glial-derived (and/or blood-borne) lactate where it serves as an energetic fuel, particularly in the setting of increased energy demands and in circumstances for which glucose supply from circulation is impaired.

Evidence in humans suggests that brain ECF lactate contributes to cerebral energy metabolism.[5] During exercise and concomitant cerebral activation, the proportion of glucose metabolism decreases in parallel with a proportional increase of lactate metabolism with subsequent increase in cerebral lactate delivery and uptake.[4] Hypoglycemia is an additional condition in which lactate can function as an alternative substrate.[6,7]

Our interest is focused on cerebral energy metabolism in patients with acute brain injury (ABI), a condition in which clinical investigation has repeatedly demonstrated a state of increased cerebral energy demand, potentially leading to cerebral glucose depletion (GD), energy dysfunction, and cerebral metabolic crisis.[8] Cerebral GD is associated with poor outcome,[9,10] implying maintenance of adequate energy supply is essential following ABI. The cerebral microdialysis (CMD) technique has greatly contributed to our understanding of cerebral energy metabolism in ABI patients and allows continuous bedside sampling of brain levels of glucose and lactate in the ECF.[11]

Dynamics of glucose and lactate levels in the ECF—which represents the environment to which neurons are exposed—have not been extensively studied in humans under conditions of varying levels of cerebral glucose. The objective of this study was to

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investigate the cerebral metabolic response to prolonged brain GD in ABI patients monitored with CMD, aiming to specifically examine the role of cerebral lactate as supplemental energy substrate in this setting. We also explored the relationships between blood and brain ECF levels of glucose and lactate in conditions of normal and low brain glucose.

Methods

Patients

This was a retrospective analysis of a prospective cohort database of ABI patients monitored with CMD from October 2009 to May 2014 at the Department of Intensive Care Medicine, Lausanne University Hospital (Centre Hospitalier Universitaire Vaudois), Lausanne, Switzerland. Patients with ABI included comatose subjects (defined by a Glasgow Coma Scale score ≤8) with severe traumatic brain injury (TBI) or poor-grade subarachnoid hemorrhage (SAH), with an abnormal computed tomography (CT) scan (for TBI, Marshall score >II; SAH, Fisher grade >2), who had an indication for intracranial monitoring consisting of CMD, brain tissue oxygen tension ($PbtO_2$), and intracranial pressure (ICP) as part of standard patient care. The study was approved by the ethical committee of the University of Lausanne, Switzerland, and waiver of consent was allowed due to the retrospective nature of the study.

Monitoring of cerebral energy metabolism

CMD consisted of a CMA 70 catheter with a 20 KDa cut-off (CMA Microdialysis AB, Stockholm, Sweden). The microdialysis probe was perfused with artificial cerebrospinal fluid via a CMA 106 pump (CMA Microdialysis AB) at a rate of 0.3 μL/min. Microdialysis samples were collected every 60 min and analyzed immediately at the bedside for brain concentrations of glucose, lactate, and pyruvate in patients' brain ECF, using a kinetic enzymatic analyzer (ISCUS flex; CMA Microdialysis AB). CMD recovery rate is estimated to be 70% of true actual cerebral concentrations.[12] The catheter was inserted in the operating room by the neurosurgeon through a triple-lumen bolt (Integra Neurosciences, Plainsboro, NJ) and placed into visually normal brain parenchyma (sub-cortical white matter) in all patients.

Adjacent to the CMD catheter, a PbtO2 probe (Licox®; Integra Neurosciences) and an ICP monitor (Codman®, Raynham, MA) also were inserted for continuous measurement of brain tissue oxygenation and ICP. A follow-up non-contrast head CT-scan was performed within 24 h to control the correct placement of intracranial monitors.

Monitoring of systemic glucose and lactate

Intra-arterial catheter was used for sampling of arterial blood glucose and lactate that were analyzed at the bedside (simultaneously to brain ECF samples) using an arterial blood gas analyzer. Systemic glucose control was achieved using intravenous insulin, setting arterial blood glucose targets at 6–8 mmol/L. Patients were treated according to standard guidelines for the management of severe TBI[13] and SAH,[14] and as recently described by our group.[15,16] Sedation was obtained with propofol and sufentanil, and data from patients who received barbiturates were removed.

Episodes of prolonged brain glucose depletion

A brain ECF concentration of glucose <1.0 mmol/L was used as the threshold for low cerebral glucose, based on recent microdialysis studies[17] and in line with our previous studies.[16] For each patient, episodes of prolonged brain GD were defined as follows: We identified all periods where CMD monitoring showed at least two or more consecutive samples with brain ECF glucose <1.0 mmol/L, preceded and followed by at least two consecutive values of brain glucose >1.0 mmol/L. This method allowed us to optimally examine spontaneous prolonged changes of brain ECF glucose and therefore to qualitatively analyze cerebral metabolic response to prolonged brain GD and blood-brain glucose and lactate correlations in ABI patients.

Data collection and processing

Data analyzed included levels of brain ECF glucose, lactate, pyruvate, lactate/pyruvate ratio (LPR), lactate/glucose ratio (LGR), $PbtO_2$, arterial blood glucose, and arterial blood lactate. All variables were examined at two separate time-points (i.e., before [baseline] and during prolonged GD). We further calculated the change (Δ, expressed in %) from baseline to GD for blood glucose, blood lactate, brain ECF glucose, and brain ECF lactate.

Statistical analysis

Statistical analysis was performed using STATA12® (STATA Corporation, College Station, TX). Variables were presented as means ± standard deviation or as medians with interquartile ranges as appropriate based on their normal distribution. Comparisons between variables were analyzed with Student's *t* or Wilcoxon tests for continuous variables and with the chi-square test for categorical variables. For correlations between blood and brain ECF levels of glucose and lactate—given repeated measurements across different subjects—a within-subjects Pearson correlation coefficient for repeated measures analysis was performed. GD episodes were categorized according to CMD concentration of LPR. The basal LPR, with a threshold of 25, was used to distinguish between preserved and presumably disturbed cerebral oxidative metabolism (LPR >25).[11,17–19] A p value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

Among a total of 63 ABI patients who underwent CMD monitoring during the study period (October 2009 to May 2014), 26 patients (18 TBI, eight SAH) who had at least one prolonged GD episode were included in the present study (Fig. 1, study flow chart). Patients' baseline characteristics are summarized in Table 1.

Cerebral metabolic response to brain glucose depletion

A total of 60 episodes with prolonged brain GD were identified with a median of 2 (range, 1–3) episodes per patient, lasting a median of 3 (range, 2–6) h.

Increased brain LPR >25 was frequently associated with GD (48/60 episodes, 80%). During GD, average $PbtO_2$ was 26 ± 6 mm Hg. In contrast to LPR, only 5/60 GD episodes (8%) displayed brain tissue hypoxia ($PbtO_2 < 15$ mm Hg); therefore, the large majority of episodes with brain GD were non-hypoxic in nature.

Compared with baseline, GD was associated with a significant increase in brain ECF concentrations of lactate (baseline 4.0 ± 2.3 vs. 5.4 ± 2.9 mmol/L during GD; $p = 0.004$), pyruvate (126.9 ± 65.1 vs. 172.3 ± 74.1 μmol/L; $p = 0.0005$), LPR (27 ± 6 vs. 35 ± 9; $p < 0.0001$) and LGR (4 ± 2 vs. 10 ± 16; $p = 0.007$; Table 2). Brain GD also was associated with lower arterial blood glucose (baseline 7.8 [7.0–8.9] vs. 6.5 [5.9–7.1] mmol/L during GD; $p < 0.0001$), while there was no significant change in arterial blood lactate (0.9 [0.8–1.1] vs. 0.9 [0.8–

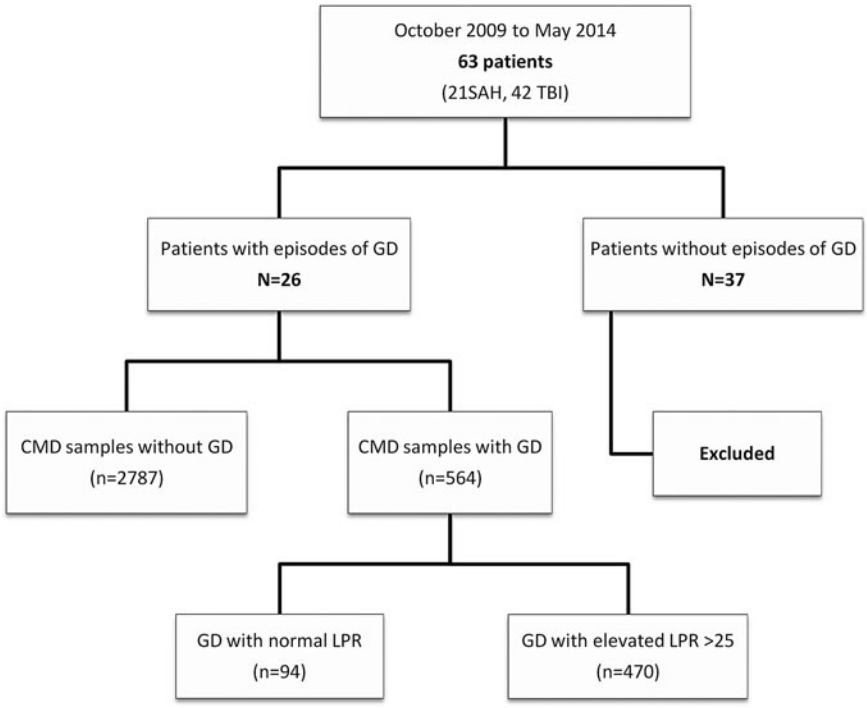

FIG. 1. Study flow chart. A total of 26 patients with prolonged cerebral glucose depletion (GD), defined as cerebral microdialysis (CMD) glucose <1 mmol/L for at least two consecutive hours, were included in the study. (LPR, lactate/pyruvate ratio; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.)

1.1] mmol/L; $p = 0.96$). No significant change in insulin infusion was observed between baseline and GD ($p = 0.18$).

Compared with baseline, brain ECF levels of glucose dropped by about 50% while brain ECF levels of lactate raised by about 50% during prolonged brain GD (Fig. 2). Blood levels of glucose and lactate did not change in the same proportion.

Relationships between blood and brain ECF levels of lactate

Correlations between arterial blood and brain ECF levels of lactate during GD are presented in Table 3. When LPR was normal, there was a strong positive correlation between blood and brain lactate (within-subjects Pearson correlation coefficient for repeated measures $r = 0.56$; $p = 0.0001$).

In contrast, when energy demand increased (LPR >25), the correlation between arterial blood and brain ECF lactate was shifted down consistently and was inversely correlated ($r = -0.11$; $p = 0.04$; Table 3).

Table 1. Patient Characteristics

Characteristics	*Value*
Number of patients	26
Brain pathology, SAH/TBI	8/18
Gender, female/male	10/16
Age, years	52 [24–57]
Admission Glasgow Coma Scale score	3 [3–7]
Time from ABI to CMD sampling, hours	11 [7–21]
Duration of CMD monitoring, days	5 [4–7]

Data are presented as median with interquartile ranges.

SAH, poor-grade aneurysmal subarachnoid hemorrhage; TBI, severe traumatic brain injury; ABI, acute brain injury; CMD, cerebral microdialysis.

Relationships between blood and brain ECF levels of glucose

A significant positive linear relationship between arterial blood and brain ECF glucose was found; however, the correlation coefficient changed according to the rate of cerebral energy demand—that is, it was shifted down from $r = 0.62$ at normal LPR to $r = 0.45$ when LPR was >25 (both, $p < 0.0001$, Table 3).

Discussion

The main findings of this study are the following: 1) prolonged brain GD was associated with a significant and physiologically relevant increase in cerebral extracellular concentrations of lactate, pyruvate, LPR, and LGR; 2) GD-related 50% increase of cerebral extracellular lactate was not paralleled with any augmentation in arterial blood lactate and was predominantly non-hypoxic; 3) compared with samples with normal brain glucose, episodes with prolonged GD were associated with lower arterial blood glucose (<7 mmol/L), which may contribute to cerebral GD after ABI; 4) in conditions of disturbed cerebral oxidative metabolism (defined by a brain LPR >25), we observed a change in the relationship between blood and brain ECF levels of glucose during GD (i.e., the linear relationship between blood and brain glucose was shifted down), suggesting increased glucose consumption and/or impaired glucose transport; and 5) the correlation coefficient between blood and brain lactate also changed consistently according to LPR level, from $r = 0.56$ at normal LPR to $r = -0.11$ when LPR was >25, mainly suggesting increased cerebral lactate delivery.

Evidence of non-hypoxic cerebral lactate production

Prolonged brain GD was associated with a significant and physiologically relevant increase in cerebral extracellular lactate that was coupled with a simultaneous rise in pyruvate and LPR. The

Table 2. Comparisons of Main Brain and Systemic Variables between Baseline (Normal Brain Glucose) and Prolonged Cerebral Glucose Depletion

Variable	*Baseline*	*Cerebral glucose depletion*	p *value*
Brain ECF glucose, mmol/L	1.3 (±0.3)	0.7 (±0.2)	< 0.0001
Brain ECF lactate, mmol/L	4.0 (±2.3)	5.4 (±2.9)	0.003
Brain ECF pyruvate, μmol/L	126.9 (±65.1)	172.3 (±74.1)	0.0005
Brain ECF lactate/pyruvate ratio	27 (±6)	35 (±9)	< 0.0001
Brain ECF lactate/glucose ratio	4 (±2)	10 (±16)	0.007
Arterial blood glucose, mmol/L	7.8 [7–8.9]	6.5 [5.9–7.1]	< 0.0001
Arterial blood lactate, mmol/L	0.9 [0.8–1.1]	0.9 [0.8–1.1]	0.96

Data are presented as means ± standard deviation or medians [interquartile range]. Concentrations of lactate, pyruvate and glucose in patients' brain extracellular fluid (ECF) were measured with a cerebral microdialysis (CMD) catheter placed in apparently normal brain. Blood arterial levels of glucose and lactate were measured with an intra-arterial catheter. Cerebral glucose depletion was defined as CMD glucose <1 mmol/L for at least two consecutive hours.

large majority of episodes with GD were associated with normal $PbtO_2$ ranges; therefore, hypoxia/ischemia was not the cause of increased lactate and LPR. An important mechanism of cerebral lactate elevation could be increased aerobic glycolysis.[15] Indeed, cerebral lactate can rise because of anaerobic glycolysis due to lack of oxygen but also, frequently, when brain oxygen is normal.[20] Subsequently, intra-cerebral lactate oxidation can yield 18 mol adenosine triphosphate (ATP) and does not require ATP, which represents an alternative energy substrate in conditions of increased demand, as seen in more than 80% of episodes of prolonged GD in this study.[2] Clearly, our findings are more in favor of non-hypoxic intra-cerebral lactate production during prolonged GD.

Correlations between blood and brain levels of lactate during episodes of GD

Further insights into the dynamics of cerebral extracellular lactate levels were provided by the analysis of the relationships between blood and brain lactate during GD. GD was associated with a significant increase in cerebral extracellular lactate levels. Increased lactate may be secondary either to a rise of blood-derived lactate or can be the result of a de novo lactate production from the brain. Since arterial blood lactate concentrations did not change significantly in any of the conditions tested, we can reasonably exclude increased systemic lactate delivery. We found a positive correlation between blood and brain lactate during GD when LPR was normal ($r = 0.56$; $p = 0.0001$). In contrast, there was an important change in the correlation between blood and brain lactate in conditions of elevated LPR, whereby the blood-brain lactate correlation coefficient became negative ($r = -0.11$; $p = 0.04$). Given blood lactate was in the normal range, this suggests the shift of the correlation coefficient may be primarily attributable to an increase in intra-cerebral lactate production to overcome elevated energy needs. Our results appear in line with previous observations in conscious human subjects,[21] as well as in patients with TBI,[8] and support the hypothesis that lactate produced within the brain parenchyma may act in these circumstances as supplemental fuel for brain cells. However, it must be pointed out that a negative correlation between brain and blood lactate during GD when LPR >25, with blood lactate in the normal range, might also be attributable to increased ECF lactate due to the change in redox and/or might be attributable to ''hyperglycolysis'' with increased uptake and

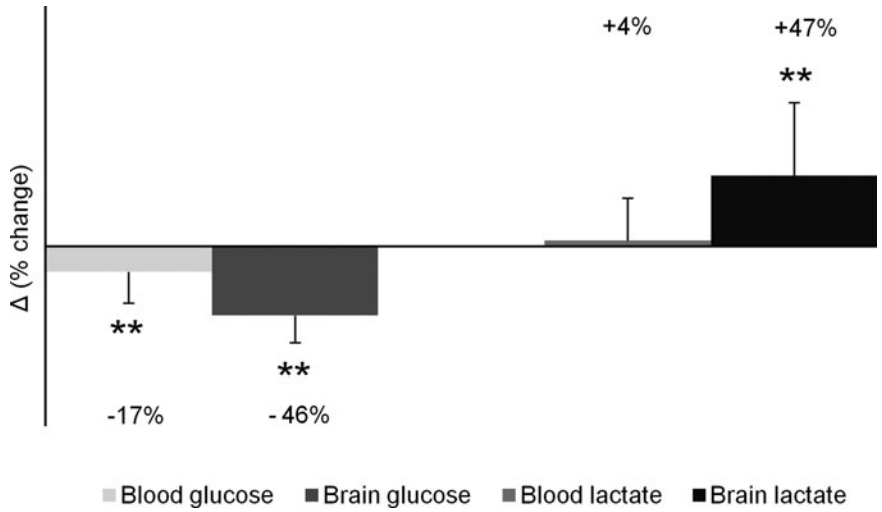

FIG. 2. Dynamic changes of blood and brain extracellular levels of glucose and lactate during prolonged cerebral glucose depletion in patients with acute brain injury. Histograms depict Δ (% changes) of arterial blood and cerebral microdialysis levels of glucose and lactate during prolonged brain glucose depletion (defined as spontaneous decreases of cerebral microdialysis glucose <1 mmol/L for at least 2 h; $n = 60$ episodes among 26 patients). $^{**}p < 0.0001$ for comparison with baseline.

Table 3. Correlations between Blood and Brain Glucose and between Blood and Brain Lactate during Episodes of Cerebral Glucose Depletion (GD), According to Cerebral Lactate/Pyruvate Ratio (LPR)

	Blood–brain glucose correlation		*Blood–brain lactate correlation*	
	r	p *value*	*r*	p *value*
GD episodes, normal LPR ≤25	0.62	<0.0001	0.56	0.0001
GD episodes, elevated LPR >25	0.45	<0.0001	−0.11	0.04

Baseline cerebral LPR represent cerebral oxidative metabolism, categorized as normal vs. impaired (LPR >25). *r* = within-subjects Pearson correlation coefficient for repeated measures. Cerebral GD was defined as cerebral microdialysis glucose <1 mmol/L for at least two consecutive hours.

glycolysis of glucose (resulting in reduced ECF glucose, i.e., GD) and increased ECF lactate produced.

What are the mechanisms of de novo cerebral lactate production? Based on the astrocyte-neuron lactate shuttle model, lactate can be produced from blood-derived glucose by astrocytes without any oxygen deficit, released in the ECF and used as an energetic substrate by neurons.[2,22] On average, the increase of cerebral lactate was delayed, compared with the drop of cerebral glucose (data not shown); therefore, elevated intra-cerebral lactate levels may be linked to reduced intra-cerebral glucose levels. This, and the fact that systemic glucose was lower during GD, supports the idea that astrocyte metabolism is activated to produce lactate. The observed increase in the LGR during GD, usually considered as a marker of astrocytic glycolysis,[11,23] is also in favor of increased astrocytic glycolysis. The analysis of Δ lactate between cerebral and arterial lactate demonstrates that the cerebral lactate increase cannot be explained by a rise in blood lactate (the latter did not change), thereby further confirming the hypothesis of activated astrocytic metabolism.

Lactate can be produced from glucose or can originate from glycogen mobilization.[1] Indeed, brain lactate can derive from glycogen stored in astrocytes, since neurons are not able to store glycogen. Astrocytes can mobilize glycogen in conditions of increased energy needs and astrocyte glycogenolysis has repeatedly been demonstrated as a source of lactate.[1,24,25] It is important to note that astrocytic glycogenolysis and glycolysis may not be mutually exclusive and can occur simultaneously as two steps of response to cerebral activation to satisfy energy needs.[1] Our findings that lactate can be used as alternative fuel after ABI is not unprecedented,[26,27] but our results support the hypothesis that lactate may be an alternative fuel in conditions of limited glucose availability and elevated energy demand, as frequently observed after ABI. In this setting, lactate might act even as a metabolic regulator by sparing glucose that can then be used for other important rescue processes, such as the pentose-phosphate pathway.[28]

Correlations between blood and brain levels of glucose

By analyzing the relationship between blood and brain glucose during episodes of GD according to baseline cerebral oxidative metabolism (dichotomized as normal vs. impaired [LPR >25]), we found that the correlation coefficient decreased when LPR was above 25. Our findings are in line with previous observations in brain-injured patients.[18] We can postulate that these changes may be the result of impaired glucose transport because of altered/disrupted blood–brain barrier or increased glucose consumption. If brain glucose transport were involved, then one would expect correlations to remain the same between blood and brain glucose whatever the time and condition. Contrary to that, we found distinct correlations according to LPR levels (Table 3), which rather suggests increased cerebral glucose consumption, in line with previous clinical investigations.[8]

The relationship between systemic glucose and brain glucose depletion

In healthy subjects, a strong linear relationship exists between systemic and cerebral glucose[29,30] while hypoglycemia is a major cause of cerebral GD.[31] Our results showed that in ABI patients, this correlation is weaker in conditions of disturbed cerebral oxidative metabolism where cerebral energy demand is higher. We hypothesize that these weaker correlations are the result of increased susceptibility of the injured brain to ''relative hypoglycemia.'' In this setting, maintenance of adequate systemic glucose supply is crucial after ABI,[10,32,33] although the definition of the exact threshold used in clinical practice is still debated. In this study, GD was associated with lower blood glucose (≈ 6–7 mmol/L) than baseline periods without GD (≈ 8–9 mmol/L), suggesting the latter threshold may be considered safer to prevent GD after ABI, as proposed by Meierhans and colleagues.[34]

Mechanisms of prolonged glucose depletion after acute brain injury

Additional mechanisms may be implicated in prolonged brain GD.[35] Hypoxia/ischemia may play a role; however, other mechanisms also have recently been identified as potential causes of GD. These include post-traumatic seizures,[36,37] cortical spreading depression,[38,39] and mitochondrial dysfunction.[40]

Study limitations

Our cohort was single-center and heterogeneous, composed of both comatose TBI and SAH patients. However, by examining data separately in the two subgroups, we found similar results (data not shown). Further, our study was not primarily focused on a single pathology but rather to examine cerebral lactate and glucose metabolism in conditions of elevated energy demand, such as those seen following ABI. For the purpose of this study, we only analyzed a selected number of data coming from the total CMD dataset that corresponded to the number of samples with prolonged brain GD. This may have introduced a selection bias and needs to be recognized as potential limitation. On the other hand, it allowed detailed characterization of the physiological response occurring when the injured brain lacks adequate glucose supply, and to specifically examine the dynamics of cerebral lactate supply and the role of lactate as potential fuel.

Another limitation of this study is that cerebral metabolism was examined regionally with CMD and $PbtO_2$, but we did not quantify brain glucose or lactate consumption with the use of neuroimaging (e.g., PET-scan or magnetic resonance spectroscopy). On the other hand, we took advantage of both semi-continuous arterial blood and CMD monitoring to characterize dynamics of glucose and lactate delivery. Our data provide an accurate assessment of the early phase of ABI during a relatively long time-window, which cannot be possible with neuroimaging. Finally, our study was primarily focused on the investigation of cerebral metabolic response to

prolonged brain GD but we did not explore potential causes of low glucose. Particularly, we did not use surface or cortical EEG for seizure or cortical spreading depression detection, nor could we assess mitochondrial function in details.

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Author Disclosure Statement

No competing financial interests exist.

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