Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: A microdialysis study*

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Objectives: **To analyze the effect of tight glycemic control with the use of intensive insulin therapy on cerebral glucose metabolism in patients with severe brain injury.**

Design: **Retrospective analysis of a prospective observational cohort.**

Setting: **University hospital neurologic intensive care unit.**

Patients: **Twenty patients (median age 59 yrs) monitored with cerebral microdialysis as part of their clinical care.**

Interventions: **Intensive insulin therapy (systemic glucose target: 4.4–6.7 mmol/L [80–120 mg/dL]).**

Measurements and Main Results: **Brain tissue markers of glucose metabolism (cerebral microdialysis glucose and lactate/pyruvate ratio) and systemic glucose were collected hourly. Systemic glucose levels were categorized as within the target "tight" (4.4–6.7 mmol/L [80–120 mg/dL]) vs. "intermediate" (6.8–10.0 mmol/L [121–180 mg/dL]) range. Brain energy crisis was defined as a cerebral microdialysis glucose <0.7 mmol/L with a lactate/pyruvate ratio >40. We analyzed 2131 cerebral microdialysis samples: tight systemic glucose levels were associated with a greater prevalence of low cerebral microdialysis glucose (65% vs. 36%, $p < 0.01$) and brain energy crisis (25% vs.17%, $p < 0.01$) than intermediate levels. Using multivariable analysis, and adjusting for intracranial pressure and cerebral perfusion pressure, systemic glucose concentration (adjusted odds ratio 1.23, 95% confidence interval [CI] 1.10–1.37, for each 1 mmol/L decrease, $p < 0.001$) and insulin dose (adjusted odds ratio 1.10, 95% CI 1.04–1.17, for each 1 U/hr increase, $p = 0.02$) independently predicted brain energy crisis. Cerebral microdialysis glucose was lower in nonsurvivors than in survivors (0.46 ± 0.23 vs. 1.04 ± 0.56 mmol/L, $p < 0.05$). Brain energy crisis was associated with increased mortality at hospital discharge (adjusted odds ratio 7.36, 95% CI 1.37–39.51, $p = 0.02$).**

Conclusions: **In patients with severe brain injury, tight systemic glucose control is associated with reduced cerebral extracellular glucose availability and increased prevalence of brain energy crisis, which in turn correlates with increased mortality. Intensive insulin therapy may impair cerebral glucose metabolism after severe brain injury. (Crit Care Med 2008; 36:3233–3238)**

KEY WORDS: glucose control; insulin therapy; brain injury; cerebral microdialysis

A substantial body of evidence supports the use of intensive insulin therapy in general critical care practice (1, 2). However, the benefit of intensive insulin therapy on the outcome of critically ill neurologic patients has not been extensively studied (3–6). Although hyperglycemia is associated with worse outcome (7–10), the optimal target for systemic glucose control is not known. This issue is important because adequate glucose supply from the systemic circulation is crucial to counteract the increase in glucose utilization and brain energy demand observed after severe brain injury (11–16).

The human brain is an obligate glucose consumer that depends on the availability of systemic glucose to maintain normal metabolism (17–19). Under conditions of fuel deprivation or other pathologic states, such as ischemia, hemorrhage, or traumatic brain injury, glucose transport may become inadequate (20–22). An excessive reduction of glucose availability may eventually contribute to compromised brain energy metabolism and aggravate neuronal injury (5, 23).

Cerebral microdialysis (CMD) is a powerful technique to detect neurochemical changes in brain interstitial tissue after severe brain injury (24) and has become the most accurate *in vivo* method to monitor brain metabolism in neurologic intensive care units (ICUs) (25). In the present work, we examined the effect of tight glycemic control on cerebral glucose metabolism using bedside continuous CMD.

METHODS

Patients. This study was conducted at the neurologic ICU, Columbia University Medical Center, NY. All patients were monitored with intraparenchymal intracranial pressure (ICP), brain tissue oxygenation ($PbtO_2$), and CMD monitoring as part of their clinical care. Patients underwent CMD if their admission Glasgow Coma Scale score (GCS) was ≤8 or they later deteriorated to this level. Retrospective analysis of medical records and clinical information system was approved by the Institutional Review Board.

General Patient Management. ICP was kept <20 mm Hg using a stepwise management strategy (i.e., cerebrospinal fluid drainage, mild hyperventilation to $Paco_2$ 30–34 mm Hg, osmotherapy with mannitol and hypertonic saline, pentobarbital infusion). Cerebral

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perfusion pressure (CPP) was targeted to avoid $PbtO_2$ <20 mm Hg and maintained >60 mm Hg. Fluid resuscitation (nondextrose containing normal and hypertonic saline solutions) and vasopressors (phenylephrine) were used as needed. Controlled normothermia (37°C) was maintained with induced cooling (Arctic Sun, Medivance, Louisville, CO).

Cerebral Microdialysis. A CMA 70 microdialysis catheter (CMA Microdialysis, Stockholm, Sweden) was inserted at the bedside through a burr-hole into the frontal lobe and secured with a triple-lumen bolt. A CMD catheter was placed into the brain parenchyma near the area of the lesioned tissue (in patients with focal injury) or in the right frontal lobe (in patients with diffuse injury). Noncontrast head CT scan was performed to confirm the placement of the CMD catheter in normal appearing white matter. The CMA 106 perfusion pump (CMA Microdialysis) was used to perfuse the catheter with sterile artificial cerebrospinal fluid at a rate of 0.3 μL/min. Samples were collected every 60 mins and analyzed for concentrations of glucose, lactate, and pyruvate with the CMA 600 analyzer (CMA Microdialysis). Sample analysis started at least 1 hr after catheter insertion to allow for normalization of changes because of probe insertion. The analyzer was automatically calibrated at the outset and every 6 hrs thereafter using standard calibration solutions. Quality controls were performed daily. Serum glucose concentrations were measured simultaneously. CPP, ICP, and GCS score were recorded hourly. CMD monitoring was discontinued at the discretion of the attending ICU physician based on the overall clinical course of the patient and perceived need for continued ICP monitoring.

Systemic Glucose Control. Systemic glucose was measured with the Sure Step Flexx system (Lifescan, Milpitas, CA) and maintained between 4.4 and 6.7 mmol/L (80–120 mg/dL) using intravenous insulin infusion (Humulin, Eli Lilly, Indianapolis, IN). Enteral nutrition (Osmolite, Ross Nutrition, Abbott Laboratories, Columbus, OH) was provided via a naso-duodenal tube starting within the first 24 hrs of admission, aiming for 25 kcal/kg/day of ideal body weight. Based on our local practices, no parenteral nutrition was given.

Analysis of Microdialysis Markers as a Function of Systemic Glucose. Values of systemic glucose were categorized into two separate ranges: "tight" (4.4–6.7 mmol/L [80–120 mg/dl]) and "intermediate" (6.8–10.0 mmol/L [121–180 mg/dl]). Values >10 mmol/L (180 mg/dL) were considered in the high range and those <4.4 mmol/L (80 mg/dL) in the low range. CMD glucose, lactate, and pyruvate were analyzed hourly. Low CMD glucose levels combined with elevated lactate/pyruvate (LP) ratio are sensitive and specific markers of compromised brain glucose metabolism (24, 25). At a perfusion rate of 0.3 μL/min, low brain glucose levels are defined as a CMD glucose <0.7 mmol/L (26–29). An LP ratio >25 is considered abnormal (24) and values >40 indicate brain energy failure with ongoing cellular injury (30). Brain energy crisis was defined as the combination of CMD glucose values <0.7 mmol/L with an LP ratio >40 (31–33).

Statistical Analysis. Univariate comparisons were performed with Student's *t*-test for continuous variables and chi-square test for categorical variables. Wide variations in CMD markers might occur over the first days of brain injury not only between different subjects but also within the same patient (28, 34–36). To account for within-subject and between-subjects variations over time and to establish independent correlations between variables, we performed a generalized estimated equations analysis using multivariable logistic regression link function and modeling within-subject dependencies with the autoregressive process (AR-1). Brain energy crisis was entered in the model as a dichotomized variable. Serum glucose, insulin dose, CPP, ICP, and GCS were entered in the model as covariates. Outcome was dichotomized as survival or death at hospital discharge. SPSS 15 software (SPSS, Chicago, IL) was used for data analysis. A p value <0.05 was considered statistically significant.

Table 1. Patients' baseline characteristics

Characteristics	Value
Total number of patients	20
Pathology	
Subarachnoid hemorrhage	10
Intracerebral hemorrhage	5
Traumatic brain injury	3
Cerebral infarction	2
Median age, yrs	59 (range 36–76)
Gender (male/female)	9/11
Median admission Glasgow Coma Scale	7 (range 3–10)
Median admission APACHE II	23 (range 14–30)
ICU length of stay, days	17 ± 6
Hospital length of stay, days	24 ± 14
Mortality	6/20 (30%)

APACHE II, Acute Physiology and Chronic Health Evaluation II; ICU, intensive care unit.

Table 2. Levels of brain glucose metabolites across all patients during cerebral microdialysis monitoring

Variables	Observed values	Normal values
CMD glucose, mmol/L	0.9 ± 0.7	1.7 ± 0.9
CMD lactate/pyruvate ratio	35 ± 21	23 ± 4
CMD/systemic glucose ratio	0.12 ± 0.09	0.4–0.5

Data are means ± SD of 2131 CMD samples. CMD, cerebral microdialysis.

Table 3. Values for intracranial pressure, cerebral perfusion pressure, and Glasgow Coma Scale score across all patients during cerebral microdialysis monitoring

Variables	Observed values	Normal values
Intracranial pressure, mm Hg	12 ± 10	6 ± 2
Cerebral perfusion pressure, mm Hg	95 ± 20	80 ± 10
Median Glasgow Coma Scale	7 (range 3–14)	15

Except otherwise stated, data represent means ± SD of 2131 hourly samples.

RESULTS

Baseline Characteristics. Baseline characteristics of the 20 consecutive patients are depicted in Table 1. All patients were mechanically ventilated and none had a previous history of diabetes. During the 1-yr study period, 2131 CMD samples were analyzed. Median duration from injury to start of CMD was 45 hrs (interquartile range 24–66 hrs) and median duration of CMD sampling was 96 hrs (interquartile range 71–162 hrs).

Values for Microdialysate Markers of Brain Glucose Metabolism across All Patients. Mean values of all CMD samples are shown in Table 2. Across all patients, CMD glucose levels and the ratio between CMD and systemic glucose were reduced, whereas high LP ratios were observed. Means of all hourly values for ICP, CPP, and GCS are shown in Table 3.

Effect of Systemic Glucose Variations on Brain Glucose Metabolism. Levels of CMD markers were analyzed according to the concentration of systemic glucose, defined as low (n = 44), tight (n = 766), intermediate (n = 1097), and high (n = 158) range. Lower CMD glucose levels (0.62 ± 0.48 mmol/L vs. 1.02 ± 0.76, $p <$ 0.001) and higher LP ratios (37 ± 22 vs. 33 ± 17, $p < 0.001$) were observed when systemic glucose was in the tight range compared with the intermediate range (Fig. 1). Levels of CMD markers at low and high systemic glucose ranges are also displayed.

Predictors of Brain Energy Crisis. The percentage of hourly measurements with either low CMD glucose levels or brain

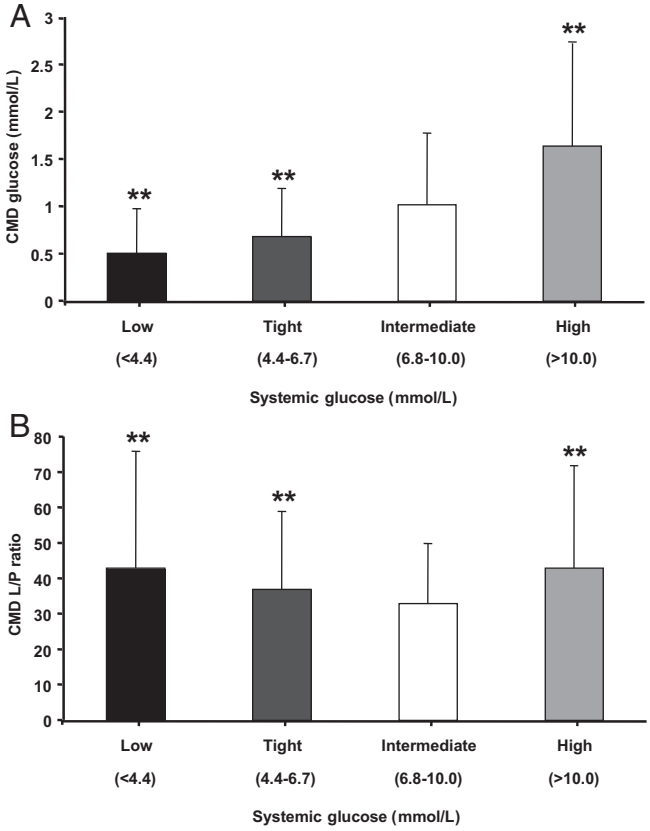

Figure 1. Histograms illustrating cerebral microdialysis (*CMD*) levels of glucose (*A*) and lactate/pyruvate (*L/P*) ratio (*B*) according to systemic glucose range. Data are expressed as means ± SD; $^{**}p < 0.01$ for comparison between intermediate systemic glucose range vs. low, tight, and high systemic glucose range.

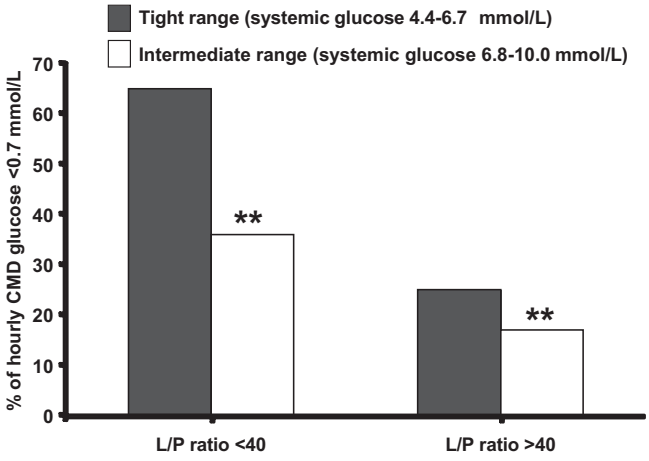

Figure 2. Histogram illustrating percentage of hourly measurements with cerebral microdialysis (*CMD*) glucose <0.7 mmol/L, in absence or presence of a lactate/pyruvate (*L/P*) ratio >40. $^{**}p < 0.01$ for comparison between tight and intermediate systemic glucose ranges.

energy crisis was significantly greater when systemic glucose was in the tight range than in the intermediate range (Fig. 2). After adjusting for ICP and CPP, lower systemic glucose levels (adjusted odds ratio 1.23, 95% confidence interval [CI] 1.10–1.37, for each 1 mmol/L decrease, $p < 0.001$) and higher insulin dose (adjusted odds ratio 1.10, 95% CI 1.04–1.17, for each 1 U/hr increase, $p = 0.02$) independently predicted brain energy crisis (Table 4).

Cerebral Microdialysis Markers and Outcome After Severe Brain Injury. Fourteen patients survived and six died at hospital discharge (one subarachnoid hemorrhage; two traumatic brain injury; three intracerebral hemorrhage). Mean CMD glucose levels were significantly lower among nonsurvivors than survivors, whereas no differences in mean systemic glucose or insulin rate were observed (Table 5). Samples (n = 196) collected during pentobarbital infusion (administered for ICP control in two patients) had lower levels of CMD glucose (0.63 ± 0.33 mmol/L vs. 0.94 ± 0.77, $p < 0.01$) and LP ratio (20 ± 4 vs. 37 ± 21, $p < 0.01$) than those without barbiturate infusion. However, when these data points (196 of 2131) were removed from the analysis, similar results were obtained. No differences in CMD glucose were found depending on the type of pathology. Furthermore, among nonsurvivors, levels of brain glucose decreased progressively during the first 5 days after ICU admission (Fig. 3). Importantly, lower CMD glucose at days 4 and 5 corresponded to lower mean GCS scores among nonsurvivors compared with survivors (4 ± 2 vs. 9 ± 2, $p < 0.01$).

After adjusting for hourly ICP, CPP, and GCS score, brain energy crisis was associated with an increased risk of death at hospital discharge (adjusted odds ratio 7.36; 95% CI 1.37–39.51; $p = 0.03$, see Table 6).

Table 4. Predictors of brain energy crisis (microdialysate glucose <0.7 mmol/L with lactate/pyruvate ratio >40)

Variable	Adjusted odds ratio (95% CI)	*p*
Systemic glucose (mmol/L)	1.23 (1.10–1.37)	<0.001
Insulin (U/hr)	1.10 (1.04–1.17)	0.02

Using a longitudinal multivariable logistic regression model that accounted for within-subject and between-subject variations over time (GEE analysis) and after adjusting for intracranial pressure and cerebral perfusion pressure, systemic glucose concentration (adjusted odds ratio 1.23, 95% confidence interval [CI] 1.10–1.37, for each 1 mmol/L decrease, $p < 0.001$) and insulin dose (adjusted odds ratio 1.10, 95% CI 1.04–1.17, for each 1U/h increase, $p = 0.02$) were independently associated with an increased rate of brain energy crisis.

DISCUSSION

In this study, we examined 2131 CMD hourly samples from 20 severely brain-injured patients. We found that: 1) the concentration of CMD glucose was frequently below normal levels and was

Table 5. Mean differences of cerebral microdialysate (CMD) glucose, systemic glucose, and insulin dose between survivors and nonsurvivors

Variable	Survivors (n = 14)	Nonsurvivors (n = 6)	*p*
CMD glucose (mmol/L)	1.04 ± 0.56	0.46 ± 0.23	0.03
Systemic glucose (mmol/L)	7.3 ± 0.8	7.6 ± 0.4	0.40
Insulin dose (U/h)	1.3 ± 0.6	1.8 ± 0.6	0.10

Data are expressed as means ± SD.

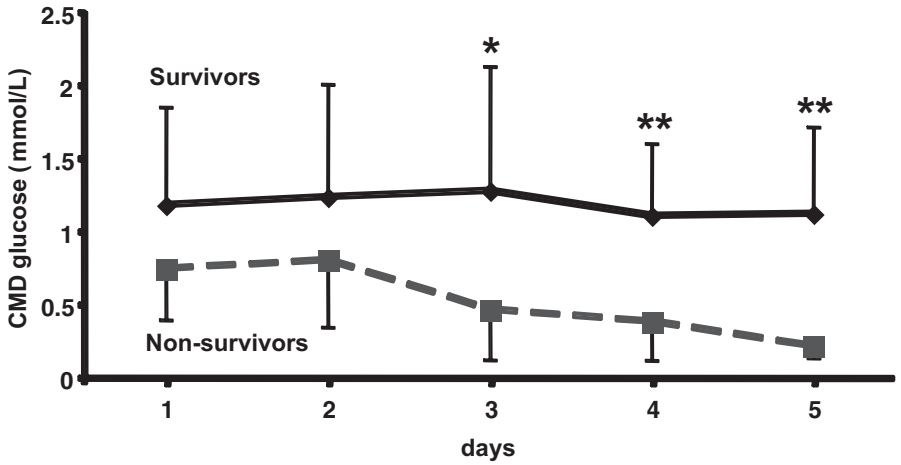

Figure 3. Line graphs illustrating means ± SD of daily medians over time for cerebral microdialysis (*CMD*) glucose in survivors and nonsurvivors. *$p < 0.05$ and **$p < 0.01$ for comparisons.

Table 6. Predictors of mortality

Variable	Adjusted odds ratio (95% confidence interval)	*p*
Brain energy crisis	7.36 (1.37–39.51)	0.02
Glasgow Coma Scale	1.12 (0.96–1.30)	0.15
Cerebral perfusion pressure	1.01 (0.97–1.04)	0.66
Intracranial pressure	1.00 (0.99–1.01)	0.91

A logistic regression model with generalized estimated equations was used to determine significant predictors of death at hospital discharge. After adjusting for covariates (including hourly intracranial pressure, cerebral perfusion pressure, and Glasgow Coma Scale), odds ratios and *p* values were calculated. Brain energy crisis was defined by the combination of a microdialysis glucose level <0.7 mmol/L and a lactate/pyruvate ratio >40.

closely associated with systemic glucose levels, 2) lower systemic glucose levels and higher insulin doses were strongly associated with brain energy crisis, and 3) brain energy crisis was associated with increased mortality at hospital discharge. These results suggest that intensive insulin therapy may impair cerebral glucose metabolism in patients with severe brain injury.

Low Brain Glucose. Low CMD glucose levels were observed in 42% of the samples analyzed, together with lower than normal brain-to-systemic glucose ratios, indicating that the availability of extracellular glucose is reduced after severe brain injury. Low brain glucose may be the consequence of several potential mechanisms, e.g., impaired glucose uptake (12, 37, 38) or, in combination with high LP ratio, may be a marker of increased anaerobic metabolism because of hypoxia/ischemia (26, 27) or mitochondrial dysfunction (30), among others. Consistent with this, 36% of the CMD glucose samples <0.7 mmol/L were observed in our patient cohort even when systemic glucose level was at the intermediate range. Our data do not allow us to definitely conclude why CMD glucose was low but consistently show a significant association between reduced systemic glucose levels and low brain glucose.

Relationship Between Brain and Systemic Glucose. We found a close relationship between systemic and brain glucose levels across a broad spectrum of different types of acute severe brain injury. This relationship is controversial and has primarily been studied in traumatic brain injury patients. Whereas some authors described a significant correlation between blood and brain glucose (39), others did not (40). Our results suggest that brain glucose levels depend on some extent on systemic levels in brain-injured patients. Variations of systemic glucose concentrations were also associated with significant elevations of LP ratio. At the extremes of systemic glucose concentrations (i.e., <4.4 mmol/L and >10 mmol/L), the highest LP ratios were observed. Reductions of systemic glucose supply might induce a decrease of CMD glucose below critical thresholds leading to increased brain anaerobic metabolism (20–22) and high LP ratio. However, high blood glucose levels for sustained periods of time after acute brain injury might promote anaerobic glycolysis, leading to tissue acidosis, accumulation of lactate, and elevated LP ratio (41–43).

Tight Glucose Control and Brain Energy Crisis. Lower levels of CMD glucose, higher LP ratios, and increased rate of brain energy crisis were observed when systemic glucose was in the tight range (4.4–6.7 mmol/L) compared with the intermediate range (6.8–10.0 mmol/L). These results indicate that, within these ranges, reduced levels of systemic glucose correlate with an increased rate of brain metabolic dysfunction, as suggested by recent animal (23) and clinical (5, 44) studies. However, other important physiologic determinants (mainly ICP and CPP) may have a substantial impact on CMD markers of brain metabolism. In this context, the higher prevalence of low CMD glucose and brain energy crisis observed at tight blood glucose range could simply be the result of higher ICP and/or lower CPP levels. For this reason, it was important to determine whether correlations between brain energy crisis and systemic glucose levels remained significant after adjusting for ICP and CPP and for within-subject and between-subjects variations over time. Using a longitudinal multivariable logistic regression analysis, we demonstrated that systemic glucose level independently predicted brain energy crisis. Specifically, in our patient cohort, for each 1 mmol/L reduction of systemic glucose an estimated 23% increased risk of brain energy crisis was found (Table 4). This risk also increased by 10% for each increase of 1 U/hr of insulin. Taken together, these data indicate that insulin-induced reduction of peripheral glucose levels, by further diminishing brain glucose availability, might

be an important and presently unrecognized cause of brain energy crisis in patients with severe brain injury. The finding that insulin dose was associated with a significantly increased risk of brain energy crisis further strengthens this view. In summary, although no definitive recommendations can be derived from our data about the exact target of blood glucose to use, the present study raises important questions about insulin therapy after severe brain injury. Although systemic glucose control is certainly very important for the management of brain-injured patients, and avoidance of hyperglycemia is mandatory, our data suggest that further research is needed to precisely determine the optimal systemic glucose target to achieve. Recent studies have shown that tight glucose control may not be of benefit for all ICU patients, e.g., those with severe sepsis (45) and a less restrictive blood glucose target (<8.2 mmol/L [150 mg/dL]) has been recommended (46). Whether this target may apply to the treatment of patients with severe brain injury warrants further study. Because of the small number of patients studied and the limitation of our retrospective study design, we wish to emphasize that we view our results as hypothesis-generating only; future changes in clinical practice should be directed by the results of larger, prospective studies designed to address this question.

Cerebral Microdialysis Markers of Brain Glucose Metabolism and Outcome. Few studies related brain glucose levels to outcome among brain-injured patients. One study found that levels of CMD glucose were significantly less in patients with traumatic brain injury who had poor outcome (47). This association was also recently confirmed in patients with subarachnoid hemorrhage (48). However, these studies did not find an independent correlation between CMD markers and outcome. Therefore, it is not clear whether brain glucose metabolites are merely markers of disease severity, or whether brain tissue glycopenia actively contributes to neurologic injury. In our cohort, CMD glucose levels were lower among those who died than in those who survived, and declined progressively over time in nonsurvivors. In addition, when adjusted for CPP, ICP, and GCS, brain energy crisis was independently associated with mortality. Although our study was not powered to answer this question, these findings suggest that CMD monitoring may prove useful as either a prognostic indicator or a target for therapy. It is also conceivable that insulin therapy in brain-injured patients might be optimally administered using a protocol that avoids critical brain tissue glycopenia or energy crisis.

Study Limitations. Our study has several limitations. First, although the data were collected prospectively, they were analyzed retrospectively. This may bias the results. However, when used, CMD was part of standard patient care, brain monitoring was started early, and a written protocol for insulin therapy was used to support our findings. Second, the number of subjects studied was small. Our data, therefore, should be considered preliminary and the findings need to be replicated in a larger patient cohort. To minimize bias, we analyzed a high number of samples and a powerful statistical model was used to account for within-subject and between-subjects variations during time. This further strengthens the study conclusions. Third, whereas insulin therapy was managed by the ICU nurses according to a written protocol, blood glucose frequently was outside the target range. However, this provided us a unique opportunity to compare the effects of "tight" and "intermediate" glucose control on cerebral glucose metabolism by having data from the same patient for each glycemic control strategy. Reductions of CMD glucose during insulin therapy may have influenced the treatment and could be a potential explanation. Our study, however, also suggests that tight glucose control may be difficult to implement in some patients with severe brain injury (48). Fourth, ongoing CMD measurements may influence the decision to withdraw care. To prevent this potential bias, investigators should ideally be blinded to CMD results. However, in our study, reduced mean CMD glucose levels corresponded to low mean GCS scores among nonsurvivors, suggesting that death was mainly related to irreversible brain injury and not to an arbitrary decision to withdraw intensive care. Therefore, we do not think that the outcome data are an epiphenomenon and the six patients who died after withdrawal of support in our study had probably experienced a devastating functional outcome. In two patients, pentobarbital infusion was associated with lower levels of CMD glucose and LP ratio. This may have been the result of reduced cerebral glucose metabolism and uptake, impaired glucose transport into the brain, or a chance finding. Although this had no significant impact on our findings, the potential effect of sedative agents on glucose metabolism should be taken into account when designing future trials using CMD monitoring.

CONCLUSION

The availability of extracellular glucose is frequently reduced after severe brain injury. Brain glucose levels seem to be closely related to systemic glucose; therefore, in our study, insulin-induced reduction of systemic glucose concentration was associated with a significant impairment in cerebral glucose metabolism. Tight systemic glucose control (4.4–6.7 mmol/L) was associated with an increased prevalence of critical brain tissue glycopenia and energy crisis compared with a less restrictive systemic glucose range (6.8 and 10.0 mmol/L). Additional larger prospective studies are needed to confirm these preliminary findings. Cerebral microdialysis may potentially be useful to monitor how insulin therapy and other therapeutic interventions affect cerebral glucose metabolism in patients with severe brain injury.

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