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Cerebral Hyperemia Measured with Near Infrared Spectroscopy during Treatment of Diabetic Ketoacidosis in Children

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Abstract

Objective—To use near infrared spectroscopy (NIRS), which indirectly detects cerebral hyperemia by measuring abnormal elevations in cerebral regional oxygen saturation (rSO₂), in children during diabetic ketoacidosis (DKA) treatment.

Study design—We randomized children 8–18 years with DKA to either more rapid or slower IV fluid treatment (n=19 total DKA episodes). NIRS was used to measure rSO₂ during DKA treatment. NIRS monitoring began as soon as informed consent was obtained and continued until the patient was transferred out of the critical care unit.

Results—rSO₂ values above the normal range (>80%) were detected in 17 of 19 DKA episodes (mean rSO₂ during initial 8 hours of DKA treatment: 86% ± 7%, range 65–95%). Elevated rSO₂ values were detected as early as the second hour of DKA treatment and persisted for as long as 27 hours. Hourly mean rSO₂ levels during treatment did not differ significantly by fluid treatment group.

Conclusions—During DKA treatment, children have elevated rSO₂ values consistent with cerebral hyperemia. Hyperemia occurs as early as the second hour of DKA treatment and may persist for 27 hours or more. Cerebral rSO₂ levels during treatment did not differ significantly in patients treated with slower versus more rapid intravenous rehydration.

Cerebral edema occurs commonly in children with diabetic ketoacidosis (DKA). Imaging studies demonstrate that mild cerebral edema can be detected in most children with DKA, but only a small fraction (0.5–1%) develop severe, life-threatening cerebral edema and cerebral injury. (1–4) It was previously assumed that children who did not have overt symptoms of brain injury during DKA treatment recovered fully, without any lasting neurological dysfunction. Results from one recent study, however, suggest that subtle deficits in memory function can be detected in children with diabetes who have experienced DKA.(5)

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Although studies demonstrate that subtle as well as more serious brain injury can be caused by DKA, the pathophysiology of this injury is poorly understood. Animal studies demonstrate reduced cerebral blood flow (CBF) in untreated DKA.(6) During DKA treatment with insulin and saline, CBF increases above normal levels.(3) This increase in CBF is accompanied by increases in the apparent diffusion coefficient of water in the brain, suggesting vasogenic edema.(3) The time of onset and duration of cerebral hyperperfusion in relation to insulin and saline treatment are not known. In addition, the effects of variations in fluid treatment regimens on the occurrence and severity of cerebral hyperperfusion have not been studied.

Near-infrared spectroscopy (NIRS) uses measurements of transmitted near-infrared light to assess regional cerebral oxygen saturation (rSO₂) in the anterior brain.(7) Abnormal elevation of rSO₂ occurs in patients with cerebral hyperemia. We used NIRS to measure rSO₂ during DKA treatment in children randomized to one of two rates of infusion of intravenous fluids. We hypothesized that more rapid rehydration might result in earlier cerebral reperfusion with earlier occurrence of hyperemia as well as more rapid return of rSO₂ to normal.

Methods

Study participants were between 8 and 18 years old, were diagnosed with type 1 diabetes mellitus, and had DKA (defined as serum glucose > 300 mg/dl, venous pH < 7.25 or serum bicarbonate < 15 mEq/l, and a positive test for urine ketones or serum ketones > 3 mmol/L). We excluded children who were transferred to the study center after beginning DKA treatment. The study was approved by the hospital institutional review board.

All patients were treated with an initial intravenous fluid bolus of 10 cc/Kg of 0.9% saline. Whenever possible, we attempted to obtain informed consent during this initial fluid bolus. If consent could not be obtained during this time, patients were started on intravenous insulin (see below) and infusion of 0.9% saline continued at 1.5 times the patients' maintenance rate until consent could be obtained. If consent could not be obtained within two hours of treatment initiation, patients were no longer considered eligible for participation.

After obtaining written informed consent from guardians, patients were randomly assigned to one of two treatment protocols. Patients randomized to study arm A (more rapid rehydration) received a second 10 cc/Kg bolus of 0.9% saline. Subsequent fluid replacement assumed a fluid deficit of 10% of body weight and aimed to replace 2/3 of this deficit over the first 24 hours of treatment, in addition to maintenance fluids. Partial replacement for ongoing urinary fluid losses was also added to the fluid rate for study arm A. Half of the volume of urine output for each two-hour period during treatment was added to the intravenous fluid rate for each subsequent 2 hour period. Replacement of urine output volume continued until the patient's serum glucose concentration declined below 250 mg/dL.

Patients randomized to study arm B (slower rehydration) received no additional boluses of 0.9% saline beyond the initial 10 cc/Kg bolus. Subsequent fluid replacement in study arm B assumed a deficit of 7% of body weight and aimed to replace this deficit evenly over a period of 48 hours in addition to maintenance fluids. Patients randomized to study arm B did not receive replacement for ongoing urinary fluid losses. For both study arms, we used 0.9% saline as the replacement fluid until the serum glucose concentration declined below 250 mg/dL, after which 0.45% saline was used. Intravenous fluid treatment was continued until

acidosis resolved (serum bicarbonate concentration above 18 mmol/L) and the patient transitioned from intravenous insulin to subcutaneous insulin therapy.

Both study arms were identical in regard to insulin treatment and patient monitoring. Continuous intravenous insulin infusion at 0.1 units/Kg/hour was begun after the initial intravenous fluid bolus. Potassium replacement was given as an equal mixture of potassium chloride and potassium phosphate at an initial dosage of 40 mEq /liter of intravenous fluid. Potassium administration rates were adjusted as necessary to maintain normal serum potassium concentrations. Treating physicians were instructed that additional fluid boluses could be administered if these were clinically necessary based on the patient's clinical status, peripheral perfusion and circulation. Similarly, treating physicians were able to raise or lower fluid infusion rates during treatment if it was felt that continuing the fluid rate prescribed by the study protocol might compromise patient safety.

Vital signs were evaluated hourly during treatment. Neurological status was assessed hourly using age-appropriate Glasgow Coma Scale (GCS) scores(8) for all patients, and every 30 minutes or more frequently for patients with altered mental status (GCS scores below 14). Serum electrolyte concentrations, venous pH, and PCO₂ were measured initially and every 3 hours; blood glucose concentrations were measured hourly until the intravenous insulin infusion was discontinued and the patient began subcutaneous insulin injections. Corrected serum sodium (Na) concentrations were calculated as: measured serum Na + 1.6 ([blood glucose concentration – 100]/100).

As soon as informed consent was obtained, we began continuous monitoring of rSO₂ using NIRS. We used the Covidien/Somanetics INVOS cerebral oximeter monitor system for rSO₂ monitoring (Somanetics Inc, Troy, MI). The left side of the patient's forehead was swabbed with alcohol and a pediatric SomaSensor probe was applied and connected to the monitor via a sensor cable. The system recorded rSO₂ values every 30 seconds and these data were used to calculate hourly mean rSO₂ values. NIRS monitoring was continued until the patient left the pediatric critical care unit, after resolution of acidosis and transition from intravenous insulin infusion to subcutaneous insulin treatment. Because this was an ancillary study to a larger parent study involving magnetic resonance imaging (MRI) during DKA treatment,(9) enrolled patients had one or more interruptions in monitoring of rSO₂. These interruptions were necessary to avoid the INVOS monitor or probe coming into proximity with the MRI scanner. As soon as possible after MRI, a new SomaSensor probe was placed on the patient's forehead and monitoring was re-started. If more than 50 percent of the rSO₂ values for any given hour were not recorded due to these interruptions, the mean value for that hour was considered to be missing (12% of the hourly values recorded). rSO₂ values were considered to be abnormal if they were above 80% or below 55%, indicating cerebral hyperperfusion or hypoperfusion, respectively.(7, 10)

Statistical Analysis

We compared biochemical and demographic characteristics for study groups A and B using the Wilcoxon rank sum test for continuous variables and the Fisher Exact test for categorical variables. Regional cerebral oxygen saturation (rSO₂) trajectories were modeled using mixed-effects linear regression models, with random intercepts used to model correlations among measurements taken during the same treatment episode.(11) Four alternative regression models for group-specific hourly mean levels (up to post-treatment hour 22, after which fewer than 8 measurements per hour were available) were fitted and compared using the Akaike information criterion.(12) Compared models included polynomial (linear or quadratic) models and broken line (one or two break point) regression models. Break point locations were specified at 8 and 14 hours, as suggested by exploratory modeling via Stata's kernel-weighted local polynomial regression command, *lpoly*. Restricted maximum

likelihood estimates of group-specific and between-group differences in adjusted mean levels from the best-fitting mixed-effects model are reported, along with 95% confidence intervals. Statistical analysis was implemented in Version 11 of Stata.(13)

Results

Eighteen patients participated. Two patients were enrolled in the study twice, therefore the study involved a total of twenty DKA episodes. Ten DKA episodes were randomized to study arm A (more rapid rehydration) and ten to study arm B (slower rehydration). One patient was withdrawn from the study before receiving the assigned fluid protocol, therefore 19 DKA episodes in total were analyzed. All patients who were enrolled in the study, including the patient who was withdrawn, recovered fully without any apparent neurological deficits.

One patient was treated for suspected cerebral edema during the course of the study. This patient (randomized to study arm A) had a decline in GCS score to 13 approximately 90 minutes after beginning DKA treatment. Thirty minutes later, the patient's GCS score declined to 12 and the patient was treated with mannitol for suspected cerebral edema. No improvement in mental status was observed after mannitol and no further treatment for cerebral edema was administered. The patient's mental status spontaneously improved at hour 6 and returned to normal by hour 9. Magnetic resonance imaging studies in this patient did not demonstrate overt signs of cerebral edema. All other patients enrolled in the study had GCS scores of 14 or 15 throughout the study period.

Biochemical data for the DKA episodes treated with each protocol are presented in the Table. Although rates of fluid administration were specified by the study arms, physicians caring for study patients were allowed to administer additional fluid boluses if they felt this was necessary to treat severe dehydration or abnormal circulatory status. Patients in both groups received greater volumes of fluids (due to administration of fluid boluses) than that specified in the study protocol. Patients in arm A received a mean of 32 ± 16 cc/Kg as fluid boluses and patients in arm B received 19 ± 10 cc/Kg (including bolus amounts specified by the study protocol and additional boluses administered based on clinical status, $p=0.05$). All patients received intravenous fluids for at least 8 hours. Thereafter, intravenous therapy was discontinued at varying times, corresponding with the time of resolution of acidosis and transition to subcutaneous insulin therapy. To compare total fluid volumes received by the groups, we therefore calculated the total intravenous fluids received during the first 8 hours of treatment only. During this 8-hour period, patients in group A received a total of 62 ± 18 cc/Kg and patients in group B received 42 ± 7 cc/Kg ($p=0.006$). Note that the greater variability in the rate of fluid administration in group A is attributable to replacement of urine output volume as dictated by the protocol.

Cerebral rSO_2 values for the 19 analyzed DKA episodes are shown in Figure 1, along with adjusted mean levels from the best-fitting regression model, a broken-line regression model with a break point at 8 hours. One patient discontinued monitoring before discharge from the critical care unit (at 6 hours) due to technical difficulties and another elected to stop participation in the study at 5 hours. All other patients underwent monitoring until discharge from the pediatric critical care unit (range 8–27 hrs).

rSO_2 values above the normal range ($rSO_2 > 80\%$) were documented in 17 of 19 episodes. Only two patients (10%) had values within the normal range throughout treatment. Due to the time required for enrollment and informed consent, the earliest rSO_2 measurements were obtained during the second hour of DKA treatment. Among 9 episodes with rSO_2 values measured in hour two, seven (78%) had values above the normal range. Five episodes (26%)

had one or more hourly mean values that were at or above the upper limit of measurement of the monitor ($rSO_2 \geq 95\%$). After 8 hours of DKA treatment, rSO_2 values tended to decline gradually, although 12 of 19 (63%) continued to be elevated above the normal range at the time of discharge from the critical care unit. Only five patients were monitored for more than 24 hours. Elevated rSO_2 values were documented (between 24–27 hours) in four of these patients. We did not detect any declines in rSO_2 values suggestive of cerebral ischemia ($rSO_2 < 45\%$). (7, 10)

Mean differences between groups in hourly rSO_2 levels derived from the regression models are shown in Figure 2. At each hour, the 95% confidence interval for mean differences between groups includes zero, indicating that the observed differences were not significant. Although the differences in hourly rSO_2 between groups were not significant, the patterns of change in rSO_2 within the groups did suggest some differences. During the first 8 hours of DKA treatment, mean values in Group A increased whereas values in Group B declined gradually (Group B v. Group A difference in hourly change for first 8 hours = -0.97 , 95% CI: -1.77 to -0.17 ; $p=0.017$). After 8 hours, values in Group A showed a trend toward more rapid decline than those of Group B. These differences were just short of statistical significance (Group B v. Group A difference in hourly change in hours 8 through 22 = 0.27 , 95% CI: -0.02 to 0.57 ; $p=0.07$). It should be noted, however, that rSO_2 values in Group A were somewhat lower at baseline compared with Group B, and that values at the 8 hour time point were similar in the two groups.

Discussion

In this study, we documented elevated cerebral rSO_2 values in children undergoing treatment for DKA, regardless of whether the children were treated with more rapid or slower intravenous fluid infusion. These findings are consistent with previous studies (3) and suggest the relatively uniform presence of cerebral hyperperfusion in children during DKA treatment. Our findings also demonstrate that cerebral hyperperfusion occurs rapidly (within 2 hours) after the initiation of insulin and fluid therapy and may persist beyond 24 hours. Although we did not detect any significant differences in hourly mean rSO_2 levels in children randomized to slower versus more rapid rehydration, the rSO_2 trajectories of the two groups differed somewhat, possibly suggesting a greater rising trend early in treatment and a faster return to normal rSO_2 values with more rapid rehydration.

The cause of DKA-related cerebral edema and cerebral injury is not well understood. Previous data suggest that cerebral edema during DKA treatment is vasogenic, (3, 14) and findings on MRI studies in children during DKA are consistent with elevated cerebral blood flow (CBF) and increased fluid in the extracellular space. (3) Regional cerebral oxygen saturation during DKA treatment in children has been evaluated previously in only one small study. (14) In that study, six children with DKA and substantial alterations in mental status underwent NIRS monitoring for 24 hours from the time of admission to the critical care unit. Similar to our findings, these children had cerebral hyperemia that decreased toward normal as the patients recovered from DKA. Unlike our study, however, eligible patients could have been treated for DKA for up to 12 hours before enrollment. Therefore, the timing of onset of cerebral hyperemia was unclear. Our data confirm these results and additionally suggest that cerebral hyperemia occurs very rapidly (within 2 hours) after initiation of DKA treatment.

To our knowledge, only two human studies evaluated CBF in individuals with DKA before initiation of treatment. In one 1947 study, six adults with severe DKA who presented in coma and eight adults with severe DKA who were confused but conscious were evaluated. (15) The comatose patients were found to have elevated CBF whereas conscious patients

had reduced CBF. In a more recent study, five children with DKA were evaluated with transcranial doppler ultrasound.(16) In these children, diastolic and mean cerebral blood velocities were lower at admission and rose above normal during DKA treatment. These differences, however, were not statistically significant in the small sample evaluated.

Recent studies in animal models demonstrate low CBF during untreated DKA (similar to the alert patients in the 1947 study by Kety et al), and an increase in CBF during DKA treatment.(6) In the Kety study, cerebral oxygen consumption was found to be substantially decreased in patients with coma and slightly decreased in alert patients compared with normal controls. Cerebral oxygen consumption was found to be inversely correlated with serum ketone concentrations.(15) These data raise the possibility that elevated rSO₂ values during DKA treatment may not only reflect increased CBF, but also may reflect reduced cerebral oxygen consumption.

Under normal circumstances, CBF is tightly regulated to maintain constant cerebral oxygen delivery.(17–19) Cerebral “autoregulation” allows CBF to remain consistent despite changes in systemic blood pressure or cerebral perfusion pressure. Regional CBF is also tightly linked to the metabolic demand of neurons, with local release of neurotransmitters and vasoactive factors causing dilation or constriction of cerebral arterioles in accordance with local need.(17–20) Failure of cerebral autoregulation may occur when systemic blood pressure exceeds the capacity of the cerebral vasculature for vasoconstriction, such as in hypertensive encephalopathy or eclampsia.(21, 22) Outside of the setting of severe hypertension, cerebral hyperemia is common mainly in conditions in which cerebral hypoperfusion is followed by reperfusion. Elevated CBF and vasogenic cerebral edema are common after stroke or traumatic brain injury,(23) and cerebral “hyperperfusion syndrome” may occur after carotid endarterectomy or stenting.(24) Reduced cerebral rSO₂ has been demonstrated during exercise in children with congenital heart disease with elevated rSO₂ above the patient’s baseline occurring within minutes after exercise cessation.(25) In addition, cerebral hyperemia has been shown to occur after prolonged hypocapnia when PCO₂ levels rise toward normal.(26, 27)

Several factors may contribute to cerebral hyperperfusion and autoregulatory failure in children undergoing treatment for DKA. Recent data suggest that cerebral hypoperfusion may occur during untreated DKA,(6, 15) and hyperemia may therefore reflect a response to reperfusion of brain tissue. Alternatively, cerebral hyperemia may occur in response to rising CO₂ concentrations during DKA treatment.(26, 27) Ketone bodies have also been proposed to have direct effects on the cerebral vasculature and on neuronal metabolism.(15, 28, 29) Beta-hydroxybutyrate exposure has been shown to stimulate production of vascular permeability factor in endothelial cells, and exposure to acetoacetate to result in increased production of endothelin-1. These data raise the possibility that CBF might be modified by changes in ketone concentrations during DKA treatment. Older studies also suggest that ketones (particularly acetoacetic acid anion) might affect cerebral metabolism, resulting in reduced cerebral oxygen consumption and declines in mental status, independent of acidosis.(15, 29) It is therefore possible that increased rSO₂ could in part reflect declines in cerebral metabolic rate associated with rising levels of acetoacetate during early DKA treatment.(30)

Although previous hypotheses focused on excessive fluid infusion and declines in serum osmolality as possible causes of cerebral edema in DKA, more recent data suggest that cerebral hypoperfusion and the effects of reperfusion during DKA treatment may be more important factors.(6, 31, 32) Our data suggest that the occurrence and extent of cerebral hyperemia during DKA treatment is not significantly affected by differences in fluid infusion rate within the range used in this study. Although rSO₂ values in the first 8 hours of treatment tended to rise in the rapid rehydration group and showed a gradual decline in the

slower rehydration group, baseline rSO₂ values were lower in patients enrolled in the former group. It is therefore possible that the observed trend simply reflected the tendency for rSO₂ values in most patients to eventually rise above normal, rather than reflecting treatment-related differences. After 8 hours, there was a trend toward more rapid normalization of rSO₂ in the rapid rehydration group, but these data similarly should be interpreted with caution given the small number of patients studied.

The current study has some limitations. Because of the delays required for enrollment and consent, patients could not begin NIRS monitoring until one to three hours after beginning DKA treatment. We therefore could not obtain data to compare rSO₂ values during untreated DKA to those during treatment. Comparison of rSO₂ curves for the treatment groups suggested different trajectories in patients treated with rapid versus slower rehydration, but baseline rSO₂ values differed between the groups and the number of patients in each group was small. Therefore, these findings should be interpreted with caution and should be confirmed in a larger study. The implications of our findings are unclear. NIRS measures venous oxygen saturation in a limited anterior region of the brain. Whether these regional data reflect similar changes throughout the brain is uncertain.^(33, 34) Data from MRI studies suggest that some brain regions may differ from others in regard to edema formation and blood flow changes during DKA treatment.⁽³⁾ It is therefore possible that some brain regions may have normal or even sub-normal blood flow and others are hyperemic. Further, because hyperemia suggests lack of appropriate coupling of CBF with oxygen demand (i.e. absence of autoregulation), it is theoretically possible that hyperemia in some brain regions could divert blood flow from other regions causing hypoperfusion (similar to the “steal” phenomenon documented in some cerebrovascular diseases).⁽³⁵⁾ This phenomenon could be particularly relevant in the setting of inadequate replacement of intravascular volume.

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References

1. Edge J, Hawkins M, Winter D, Dunger D. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child*. 2001; 85:16–22. [PubMed: 11420189]
2. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, et al. Risk Factors for Cerebral Edema in Children with Diabetic Ketoacidosis. *N Engl J Med*. 2001; 344:264–269. [PubMed: 11172153]
3. Glaser N, Gorges S, Marcin J, Buonocore M, DiCarlo J, Neely E, et al. Mechanism of Cerebral Edema in Children with Diabetic Ketoacidosis. *J Pediatr*. 2004; 145:164–171. [PubMed: 15289761]
4. Krane E, Rockoff M, Wallman J, Wolfsdorf J. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med*. 1985; 312:1147–1151. [PubMed: 3920521]
5. Ghatti S, Lee J, Holtpatrick C, DeMaster D, Glaser N. Diabetic ketoacidosis and memory impairment in children with Type 1 diabetes. *J Pediatr*. 2010; 156:109–114. [PubMed: 19833353]
6. Yuen N, Anderson S, Glaser N, O'Donnell M. Cerebral Blood Flow and Cerebral Edema in Rats with Diabetic Ketoacidosis. *Diabetes*. 2008; 57:2588–2594. [PubMed: 18633109]
7. Madsen P, Secher N. Near-infrared oximetry of the brain. *Progress in Neurobiol*. 1999; 58:541–560.

8. Reilly P, Simpson D, Sprod R, Thomas L. Assessing the conscious level in infants and young children: a paediatric version of the Glasgow Coma Scale. *Child's Nerv Syst.* 1988; 4:30–33. [PubMed: 3135935]
9. Glaser N, Wooton-Gorges S, Buonocore M, Tancredi D, Marcin J, Caltagirone R, et al. Subclinical cerebral edema in children with diabetic ketoacidosis randomized to 2 different rehydration protocols. *Pediatrics.* 2013; 131:e73–e80. [PubMed: 23230065]
10. Ghanayem N, Wernovsky G, Hoffman G. Near-infrared spectroscopy as a hemodynamic monitor in critical illness. *Pediatr Crit Care Med.* 2011; 12(Suppl):S27–S32. [PubMed: 22129547]
11. Ciftci K, Sankur B, Kahya YP, Akin A. Multilevel statistical inference from functional near-infrared spectroscopy data during stroop interference. *IEEE Trans Biomed Eng.* 2008 Sep; 55(9): 2212–2220. [PubMed: 18713690]
12. Burnham, K.; Anderson, D. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach.* second ed. New York: Springer-Verlag; 2002.
13. StataCorp. *Stata Statistical Software: Release 11.* College Station, TX: Stata Corporation LP; 2009.
14. Roberts J, Vavilala M, Schenkman K, Shaw D, Martin L, Lam A. Cerebral hyperemia and impaired cerebral autoregulation associated with diabetic ketoacidosis in critically ill children. *Crit Care Med.* 2006; 34:2217–2223. [PubMed: 16763506]
15. Kety S, Polis B, Nadler C, Schmidt C. The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. *J Clin Invest.* 1947; (27):500–510.
16. Hoffman W, Pluta R, Fisher A, Wagner M, Yanovski J. Transcranial doppler ultrasound assessment of intracranial hemodynamics in children with diabetic ketoacidosis. *J Clin Ultrasound.* 1995; 23:517–523. [PubMed: 8537473]
17. Cipolla, M. *The Cerebral Circulation.* San Rafael, CA: Morgan & Claypool Life Sciences; 2009.
18. Attwell D, Buchan A, Charkpak S, Lauritzen M, MacVicar B, Newman E. Glial and neuronal control of brain blood flow. *Nature.* 2010; 468:232–243. [PubMed: 21068832]
19. Jaspersen S, Ostergaard L. The roles of cerebral blood flow, capillary transit time heterogeneity, and oxygen tension in brain oxygenation and metabolism. *J Cereb Blood Flow and Metab.* 2011; 32:264–277. [PubMed: 22044867]
20. Stocchetti N, Maas A, Chieragato A, van der Plas A. Hyperventilation in head injury: a review. *Chest.* 2005; 127:1812–1827. [PubMed: 15888864]
21. Cipolla M, Bishop N, Chan S. Effect of pregnancy on autoregulation of cerebral blood flow in anterior versus posterior cerebrum. *Hypertension.* 2012 ePub ahead of print.
22. Utsunomiya H. Diffusion MRI abnormalities in pediatric disorders. *Brain & Development.* 2011; 33:235–242. [PubMed: 20880644]
23. Marchal G, Young A, Baron J. Early postischemic hyperperfusion: Pathophysiologic insights from positron emission tomography. *J Cereb Blood Flow Metab.* 1999; 19:467–482. [PubMed: 10326714]
24. Lieb M, Shah U, Hines G. Cerebral hyperperfusion syndrome after carotid intervention: a review. *Cardiol Rev.* 2012; 20:84–99. [PubMed: 22183061]
25. Danduran M, Dixon J, Rao R. Near infrared spectroscopy describes physiologic payback associated with excess postexercise oxygen consumption in healthy controls and children with complex congenital heart disease. *Pediatr Cardiol.* 2012; 33:95–102. [PubMed: 21892649]
26. Curley G, Kavanagh B, Laffey J. Hypocapnia and the injured brain: More harm than benefit. *Crit Care Med.* 2010; 38:1348–1359. [PubMed: 20228681]
27. Muizelaar J, Marmarou A, Ward J, Kontos H, Choi S, Becker D, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg.* 1991; 75:731–739. [PubMed: 1919695]
28. Isales C, Min L, Hoffman W. Acetoacetate and B-hydroxybutyrate differentially regulate endothelin-1 and vascular endothelial growth factor in mouse brain microvascular endothelial cells. *J Diab Comp.* 1999; 13(2):91–97.
29. Schneider R, Doroller H. Relative importance of ketosis and acidosis in production of diabetic coma. *Quart J Exper Physiol.* 1938; 28:323–333.

30. Wootton-Gorges S, Buonocore M, Kuppermann N, Marcin J, DiGirolamo M, Neely E, et al. Detection of cerebral {beta}-hydroxy butyrate, acetoacetate, and lactate on proton MR spectroscopy in children with diabetic ketoacidosis. *Am J Neuroradiol.* 2005; 26:1286–1291. [PubMed: 15891198]
31. Glaser N, Marcin J, Wootton-Gorges S, Buonocore M, Rewers A, Strain J, et al. Correlation of Clinical and Biochemical Findings with DKA-related Cerebral Edema in Children using Magnetic Resonance Diffusion Weighted Imaging. *J Pediatr.* 2008; 153:541–546. [PubMed: 18589447]
32. Glaser N, Yuen N, Anderson S, Tancredi D, O'Donnell M. Cerebral Metabolic Alterations in Rats with Diabetic Ketoacidosis: Effects of Treatment with Insulin and Intravenous Fluids and Effects of Bumetanide. *Diabetes.* 2010; 59:702–709. [PubMed: 20028943]
33. Durandy Y, Rubatti M, Couturier R. Near infrared spectroscopy during pediatric cardiac surgery: errors and pitfalls. *Perfusion.* 2012; 26:441–446. [PubMed: 21593082]
34. Taussky P, O'Neal B, Daugherty W, Luke S, Thorp D, Pooley R, et al. Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain-injured patients. *Neurosurg Focus.* 2012; 32:E2.
35. Taylor C, Selman W, Ratcheson R. Steal affecting the central nervous system. *Neurosurgery.* 2002; 50:688–689.

Figure 1. Regional cerebral oxygen saturation (rSO₂) during DKA treatment in children
Individual episode trajectories are depicted along with hourly means (hollow squares) and 95% confidence intervals for hourly means (represented by large polygon) derived from the regression model. The estimated standard deviation of the between-episode random intercepts is 5.5 and of the residuals is 4.6, resulting in an intra-episode correlation coefficient of 60%, indicating a moderately high level of consistency in individual rSO₂ values in individual patients.

Group B vs. Group A Differences (95% CI) in Hourly Mean Percentage Regional Cerebral Oxygen Saturation From Mixed-Effects Regression Model

Figure 2. Regional cerebral oxygen saturation (rSO₂) during DKA treatment. Mean differences in hourly levels for Group B (slower rehydration) versus Group A (more rapid rehydration)
 Point estimates (hollow diamonds) and 95% confidence intervals for mean difference (Group B minus Group A) in hourly means from the regression model. All 95% confidence intervals include zero, indicating no significant differences between groups.

Table

Demographic and Biochemical Data at DKA Presentation for Study Patient Episodes

	Group A (n=9)	Group B (n=10)
Age, years	12 (9–17)	15 (9–18)
Male sex, %	5 (56%)	6 (60%)
New-onset diabetes, %	1 (11%)	1 (10%)
Serum glucose, mg/dL	654 (319–1165)	557 (347–986)
pH	7.13 (6.94–7.2)	7.12 (6.96–7.26)
pCO₂	22 (14–36)	22 (19–32)
Serum sodium, mmol/L	132 (120–141)	133 (132–149)
Serum potassium, mmol/L	5.0 (3.9–6.3)	5.0 (3.9–7.2)
Serum chloride, mmol/L	97 (82–104)	96 (90–101)
Serum bicarbonate, mmol/L	9 (5–14)	8.5 (5–12)
Serum urea nitrogen, mmol/L	21 (14–46)	20 (14–30)

*
Data presented as median (range)