

WORKSHEET for PROPOSED Evidence-Based GUIDELINE RECOMMENDATIONS

Worksheet Author:	Taskforce/Subcommittee: __BLS __ACLS x PEDS __ID __PROAD __x_Other: N
Author's Home Resuscitation Council: __x_AHA __ANZCOR __CLAR __ERC __HSFC __HSFC __RCSA __IAHF __Other:	Date Submitted to Subcommittee: 5/21/04

STEP 1: STATE THE PROPOSAL. Revision to current statement.

Existing guideline, practice or training activity, or new guideline: Revision to current guideline

Check the blood glucose level during stabilization after resuscitation

Step 1A: Refine the question; state the question as a positive (or negative) hypothesis. State proposed guideline recommendation as a specific, positive hypothesis. Use single sentence if possible. Include type of patients; setting (in-/out-of-hospital); specific interventions (dose, route); specific outcomes (ROSC vs. hospital discharge).

Maintaining blood glucose concentrations in the high-normal range improves neurologic outcome after perinatal asphyxia and resuscitation.

Step 1B: Gather the Evidence; define your search strategy. Describe search results; describe best sources for evidence.

Key words used included "glucose or hypoglycemia or hyperglycemia" and brain and hypoxia or ischemia or asphyxia or resuscitation and newborn or neonate or infant or perinatal

List electronic databases searched (at least AHA EndNote 7 Master library [<http://ecc.heart.org/>], Cochrane database for systematic reviews and Central Register of Controlled Trials [<http://www.cochrane.org/>], MEDLINE

[<http://www.ncbi.nlm.nih.gov/PubMed/>], and Embase), and hand searches of journals, review articles, and books.

Medline (PubMed), Old Medline (NLM Gateway), ISI Science Citation Index, EBM Reviews--Cochrane Database of Systematic Reviews, references of several review articles, personal files

- State major criteria you used to limit your search; state inclusion or exclusion criteria (e.g., only human studies with control group? no animal studies? N subjects > minimal number? type of methodology? peer-reviewed manuscripts only? no abstract-only studies?)

No abstracts

studies in adult animal models and clinical studies in adults excluded

- Number of articles/sources meeting criteria for further review: Create a citation marker for each study (use the author initials and date or Arabic numeral, e.g., "Cummins-1"). If possible, please supply file of best references; EndNote 6+ required as reference manager using the ECC reference library.

19 articles included in review

STEP 2: ASSESS THE QUALITY OF EACH STUDY

Step 2A: Determine the Level of Evidence. For each article/source from step 1, assign a level of evidence—based on study design and methodology.

Level of Evidence	Definitions (See manuscript for full details)
Level 1	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
Level 2	Randomized clinical trials with smaller or less significant treatment effects
Level 3	<u>Prospective</u> , controlled, non-randomized, cohort studies
Level 4	<u>Historic</u> , non-randomized, cohort or case-control studies
Level 5	<u>Case series</u> ; patients compiled in serial fashion, lacking a control group
Level 6	Animal studies or mechanical model studies
Level 7	Extrapolations from existing data collected for other purposes, theoretical analyses
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

Step 2B: Critically assess each article/source in terms of research design and methods.

Was the study well executed? Suggested criteria appear in the table below. Assess design and methods and provide an overall rating. Ratings apply within each Level; a Level 1 study can be excellent or poor as a clinical trial, just as a Level 6 study could be excellent or poor as an animal study. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study. For more detailed explanations please see attached assessment form.

Component of Study and Rating	Excellent	Good	Fair	Poor	Unsatisfactory
Design & Methods	Highly appropriate sample or model, randomized, proper controls AND Outstanding accuracy, precision, and data collection in its class	Highly appropriate sample or model, randomized, proper controls OR Outstanding accuracy, precision, and data collection in its class	Adequate, design, but possibly biased OR Adequate under the circumstances	<i>Small or clearly biased population or model</i> OR <i>Weakly defensible in its class, limited data or measures</i>	<i>Anecdotal, no controls, off target end-points</i> OR <i>Not defensible in its class, insufficient data or measures</i>

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint

B = Survival of event D = Intact neurological survival

Step 2C: Determine the direction of the results and the statistics: supportive? neutral? opposed?

DIRECTION of study by results & statistics:	SUPPORT the proposal	NEUTRAL	OPPOSE the proposal
Results	Outcome of proposed guideline superior, to a clinically important degree, to current approaches	Outcome of proposed guideline no different from current approach	Outcome of proposed guideline inferior to current approach

Step 2D: Cross-tabulate assessed studies by a) level, b) quality and c) direction (ie, supporting or neutral/ opposing); **combine and summarize.** Exclude the *Poor* and *Unsatisfactory* studies. Sort the *Excellent*, *Good*, and *Fair* quality studies by both *Level and Quality of evidence*, and *Direction of support* in the summary grids below. Use citation marker (e.g. author/ date/source). In the *Neutral* or *Opposing* grid use bold font for *Opposing* studies to distinguish them from merely neutral studies. Where applicable, please use a superscripted code (shown below) to categorize the primary endpoint of each study.

Supporting Evidence

	Good						Sheldon 1992 LeBlanc 1993 LeBlanc 1994 Vannucci 1996 Park 2001	LeBlanc 1997	
	Fair								
		1	2	3	4	5	6	7	8
		Level of Evidence							

A = Return of spontaneous circulation C = Survival to hospital discharge E = Other endpoint
 B = Survival of event D = Intact neurological survival

REVIEWER’S PERSPECTIVE AND POTENTIAL CONFLICTS OF INTEREST: Briefly summarize your professional background, clinical specialty, research training, AHA experience, or other relevant personal background that define your perspective on the guideline proposal. List any potential conflicts of interest involving consulting, compensation, or equity positions related to drugs, devices, or entities impacted by the guideline proposal. Disclose any research funding from involved companies or interest groups. State any relevant philosophical, religious, or cultural beliefs or longstanding disagreements with an individual.

Board-certified neonatologist and medical school faculty member for more than 10 years. Research over the past 14 years on mechanisms of brain injury in the newborn, and specifically on hypoglycemic brain injury and the role of glucose availability in hypoxic brain injury. I have no conflicts of interest

REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK: Summarize your final evidence integration and the rationale for the class of recommendation. Describe any mismatches between the evidence and your final Class of Recommendation. “Mismatches” refer to selection of a class of recommendation that is heavily influenced by other factors than just the evidence. For example, the evidence is strong, but implementation is difficult or expensive; evidence weak, but future definitive evidence is unlikely to be obtained. Comment on contribution of animal or mechanical model studies to your final recommendation. Are results within animal studies homogeneous? Are animal results consistent with results from human studies? What is the frequency of adverse events? What is the possibility of harm? Describe any value or utility judgments you may have made, separate from the evidence. For example, you believe evidence-supported interventions should be limited to in-hospital use because you think proper use is too difficult for pre-hospital providers. Please include relevant key figures or tables to support your assessment.

Most studies in newborn animal models have shown that low glucose concentration before or after hypoxia-ischemia is associated with more significant alterations in brain metabolism, poorer neurologic outcome, decreased survival, and/or increased histologic brain injury(Hattori, 1990, Yager, 1992, Park, 1995). However, some studies show no differences between hypoglycemic and normoglycemic animals (Chang, 1999. Conversely, several studies have shown some benefit to hyperglycemia during and/or after hypoxia-ischemia, but others have shown no benefit or even an increase in brain injury (Voorhies, 1986, Sheldon, 1992, LeBlanc, 1994) The major limitations of the studies reviewed are the lack of clinical correlation and the wide range of glucose values used in the studies. Glucose administration, rather than glucose concentration, was standardized in most studies. This is particularly an issue with regard to the question of whether hyperglycemia, rather than normoglycemia, might be beneficial post-resuscitation. Since blood glucose studies in hyperglycemic experiments ranged from 200 mg/dl to 600 mg/dl, it is impossible to generate a consensus statement about the effect of hyperglycemia. However, there have been no studies in the newborn that demonstrate a benefit of hypoglycemia post-asphyxia. This is in direct contrast to data from adult patients and animal models that demonstrate better outcomes after stroke in hypoglycemic patients.

Preliminary draft/outline/bullet points of Guidelines revision: Include points you think are important for inclusion by the person assigned to write this section. Use extra pages if necessary.

Attachments:

Bibliography in electronic form using the Endnote Master Library. It is recommended that the bibliography be provided in annotated format. This will include the article abstract (if available) and any notes you would like to make providing specific comments on the quality, methodology and/or conclusions of the study.

Citation List

Citation Marker	Full Citation*
Holowach-Thurston, 1974	J. Holowach-Thurston, R. E. Hauhart, and E. M. Jones. Anoxia in mice: Reduced glucose in brain with normal or elevated glucose in plasma and increased survival after glucose treatment. <i>Pediatr.Res.</i> 8:238-243, 1974.
Vannucci, 1978	R. C. Vannucci and S. J. Vannucci. Cerebral carbohydrate metabolism during hypoglycemia and anoxia in newborn rats. <i>Ann.Neurol.</i> 4 (1):73-79, 1978.
Voorhies, 1986	T. M. Voorhies, D. Rawlinson, and R. C. Vannucci. Glucose and perinatal hypoxic-ischemic brain damage in the rat. <i>Neurol.</i> 36:1115-1118, 1986.
Hattori, 1990	H. Hattori and C. G. Wasterlain. Posthypoxic glucose supplement reduces hypoxic-ischemic brain damage in the neonatal rat. <i>Ann.Neurol.</i> 28:122-128, 1990.
Rosenberg, 1990	A. A. Rosenberg and E. Murdaugh. The effect of blood glucose concentration on postasphyxia cerebral hemodynamics in newborn lambs. <i>Pediatr.Res.</i> 27:454-459, 1990.
Yager, 1992	J. Y. Yager, D. F. Heitjan, J. Towfighi, and R. C. Vannucci. Effect of insulin-induced and fasting hypoglycemia on perinatal hypoxic-ischemic brain damage. <i>Pediatr.Res.</i> 31:138-142, 1992.
Laptook, 1992	A. R. Laptook, R. J. T. Corbett, O. Arencibia-Mireles, and J. Ruley. Glucose-associated alterations in ischemic brain metabolism of neonatal piglets. <i>Stroke</i> 23:1504-1511, 1992.
Sheldon, 1992	R. A. Sheldon, J. C. Partridge, and D. M. Ferriero. Postischemic hyperglycemia is not protective to the neonatal rat brain. <i>Pediatr.Res.</i> 32:489-493, 1992.
LeBlanc, 1993	M. H. LeBlanc, M. Huang, V. Vig, D. Patel, and E. E. Smith. Glucose affects the severity of hypoxic-ischemic brain injury in newborn pigs. <i>Stroke</i> 24:1055-1062, 1993.
Tuor, 1993	Tuor, U. I., C. S. Simone, et al. (1993). Glucocorticoid prevention of neonatal hypoxic-ischemic damage: role of hyperglycemia and antioxidant enzymes. <i>Brain Res</i> 604(1-2): 165-72.
LeBlanc, 1994	M. H. LeBlanc, M. Huang, D. Patel, E. E. Smith, and M. Devidas. Glucose given after hypoxic ischemia does not affect brain injury in piglets. <i>Stroke</i> 25 (7):1443-1447, 1994.
Laptook, 1994	Laptook, A. R., R. J. Corbett, et al. (1994). The effects of systemic glucose concentration on brain metabolism following repeated brain ischemia. <i>Brain Res</i> 638(1-2): 78-84.
McGowan, 1995	J. E. McGowan, P. J. Marro, O. P. Mishra, and M. Delivoria-Papadopoulos. Brain cell membrane function during hypoxia in hyperglycemic newborn piglets. <i>Pediatr.Res.</i> 37:133-139, 1995.
Park, 1995	T. S. Park, E. R. Gonzales, A. R. Shah, and J. M. Gidday. Hypoglycemia selectively abolishes hypoxic reactivity of pial arterioles in piglets: role of adenosine. <i>Am.J Physiol</i> 268 (2 Pt 2):H871-H878, 1995.
Lin, 1996	Y. Lin and G. Greisen. Analysis of the risk of brain damage in asphyxiated infants. <i>J Perinat.Med.</i> 24 (6):581-589, 1996.

Vannucci, 1996	R. C. Vannucci, A. Rossini, and J. Towfighi. Effect of hyperglycemia on ischemic brain damage during hypothermic circulatory arrest in newborn dogs. <i>Pediatr.Res.</i> 40 (2):177-184, 1996.
LeBlanc, 1997	M. H. LeBlanc, X. B. Qian, and Z. W. Cai. The effect of glucose during ischemia on brain ATP, lactate, and glutamate in piglets. <i>Biol.Neonate</i> 72 (4):243-254, 1997.
Brambrink, 1999	A. M. Brambrink, R. N. Ichord, L. J. Martin, R. C. Koehler, and R. J. Traystman. Poor outcome after hypoxia-ischemia in newborns is associated with physiological abnormalities during early recovery. Possible relevance to secondary brain injury after head trauma in infants. <i>Exp.Toxicol.Pathol.</i> 51 (2):151-162, 1999.
Chang, 1999	Y. S. Chang, W. S. Park, S. Y. Ko, M. J. Kang, J. M. Han, M. Lee, and J. Choi. Effects of fasting and insulin-induced hypoglycemia on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. <i>Brain Res.</i> 844 (1-2):135-142, 1999.
Park, 2001	W. S. Park, Y. S. Chang, and M. Lee. Effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after acute transient global hypoxia-ischemia in the newborn piglet. <i>Brain Res.</i> 901 (1-2):102-108, 2001.

*Type the citation marker in the first field and then paste the full citation into the second field. You can copy the full citation from EndNote by selecting the citation, then copying the FORMATTED citation using the short cut, Ctrl-K. After you copy the citation, go back to this document and position the cursor in the field, then paste the citation into the document (use Ctrl-V). For each new citation press Tab to move down to start a new field.

Annotated bibliography:

J. Holowach-Thurston, R. E. Hauhart, and E. M. Jones. Anoxia in mice: Reduced glucose in brain with normal or elevated glucose in plasma and increased survival after glucose treatment. *Pediatr.Res.* 8:238-243, 1974.

Comment: *Glucose administration increased survival under anoxic conditions in newborn mice.*

R. C. Vannucci and S. J. Vannucci. Cerebral carbohydrate metabolism during hypoglycemia and anoxia in newborn rats. *Ann.Neurol.* 4 (1):73-79, 1978.

The cerebral metabolic responses to perinatal hypoglycemia and anoxia were studied in newborn rats given regular insulin (30 units per kilogram of body weight). Animals were observed for up to 2 hours with no apparent ill effects in spite of blood glucose concentrations of 0.75 mmol per liter. When exposed to 100% nitrogen at 37 degrees C, hypoglycemic animals survived only one-tenth as long as littermate controls with normal blood glucose levels (4.7 mmol/L). Pretreatment of hypoglycemic rats with glucose (10 mmol/kg) 10 and 30 minutes prior to nitrogen exposure nearly completely reversed the anoxic vulnerability. Hypoglycemia led to progressive reductions in cerebral glycogen and glucose; however, only glucose reverted to normal levels 20 minutes after systemic glucose administration. The glycolytic intermediates glucose 6-phosphate and lactate were also lower during hypoglycemia. Brain glucose levels below 0.1 mmol per kilogram were associated with a disrupted cerebral energy state, reflected by declines in phosphocreatine (33%) and

adenosine triphosphate (ATP) (10%). Cerebral energy utilization (metabolic rate) was minimally reduced (-7.2%) by hypoglycemia and returned to the control value (2.36 mmol approximately P/kg/min) with glucose treatment. The cerebral energy reserves ATP, adenosine diphosphate, and phosphocreatine declined more rapidly and to a lower level in hypoglycemic rats subjected to 2 1/2 minutes of anoxia than in normoglycemic animals rendered similarly hypoxic. The findings suggest that decreased anoxic resistance of hypoglycemic newborn rats is not primarily a function of reduced brain glycogen or altered cerebral metabolic rate. The presence of endogenous cerebral glucose stores combined with continued circulating glucose (cerebrovascular perfusion) appear to be critical factors for maintaining perinatal hypoxic survival.

Comments: Animal study with glucose pretreatment. Blood glucose concentrations in the hypoglycemia group were not regulated and varied considerably, making it impossible to determine the blood glucose level associated with decreased survival.

Level of Evidence 6

Quality Good

Evidence - Supportive

T. M. Voorhies, D. Rawlinson, and R. C. Vannucci. Glucose and perinatal hypoxic-ischemic brain damage in the rat. *Neurol.* 36:1115-1118, 1986.

Seven-day postnatal rats were rendered hyperglycemic by the SC injection of 50% glucose, following which they were exposed to hypoxia with 8% oxygen. The glucose-treated animals survived more than twice as long as saline-treated littermates. Other hyperglycemic and control rat pups were subjected to hypoxia-ischemia by unilateral common carotid artery occlusion combined with 2 hours of hypoxia. Neuropathologic analysis of recovered animals at 30 days of age showed that the brains of the glucose-treated animals were no more damaged than those of the saline controls (p greater than 0.05). The finding indicates that, unlike adults, glucose supplementation and its associated hyperglycemia in the immature rat does not increase the extent of hypoxic-ischemic brain damage.

Comments: Animal study with glucose pretreatment. No deleterious effects of hyperglycemia during hypoxia-ischemia, in direct contrast to adult data. Glucose concentrations varied in experimental animals; 7-day rat model may not be equivalent to perinatal asphyxia.

H. Hattori and C. G. Wasterlain. Posthypoxic glucose supplement reduces hypoxic-ischemic brain damage in the neonatal rat. *Ann. Neurol.* 28:122-128, 1990.

We evaluated the effect of posthypoxic glucose supplement in a neonatal hypoxic-ischemic animal model. Seven-day-old rats underwent bilateral ligation of the carotid arteries, followed by exposure to an 8% oxygen atmosphere for 1 hour. The extent of hypoxic-ischemic brain damage was assessed histologically 72 hours later. Glucose load immediately after the end of the hypoxic exposure reduced the volume of neocortical infarction to 37% of the unsupplemented value, and attenuated ischemic damage in the striatum and the dentate gyrus. At the end of the hypoxic exposure, the brain level of glucose was 0.3 mmol/kg and the level of lactate 9 mmol/kg. Glucose supplement produced a rapid rise in brain glucose level to 3 to 5 mmol/kg over the next 2 hours. Lactate in both brain and plasma gradually fell

toward the baseline level during the first hour of recovery. Posthypoxic glucose supplement slightly retarded lactate restitution. At any period of this neonatal model, brain lactate levels did not exceed the toxic level, which is postulated to be responsible for cerebral infarction in adult ischemic models. These results illustrate the important role of glucose in the development of neonatal hypoxic-ischemic encephalopathy and the fact that full cortical infarction can develop even if brain lactate levels are low.

Comments: Animal study with treatment immediately after insult; demonstrated efficacy of post-insult glucose administration. Model may not be equivalent to perinatal asphyxia.

Level of Evidence 6

Quality Good

Evidence - Supportive

A. A. Rosenberg and E. Murdaugh. The effect of blood glucose concentration on postasphyxia cerebral hemodynamics in newborn lambs. *Pediatr.Res.* 27:454-459, 1990. The effect of preasphyxia blood glucose concentration on postasphyxia (PA) cerebral hemodynamics was examined in 21 newborn lambs. Glucose was unregulated in one group (n = 7), and controlled throughout the study by glucose clamp in hyperglycemic (n = 7) and hypoglycemic (n = 7) groups. Cerebral blood flow, determined using radiolabelled microspheres, and arterial and sagittal sinus O₂ contents were measured at control, 5 min, 1, 2, and 4 h after resuscitation from an asphyxial insult. Preasphyxia blood glucoses were 6.48 +/- 0.55 mM (mean +/- SEM), 12.08 +/- 0.80, and 2.66 +/- 0.14 in the three study groups. In all three groups, 5 min PA cerebral blood flow was significantly increased from control. In the late period after asphyxia, the unregulated group had decreased cerebral blood flow compared with control, 53.2 +/- 3.8 mL.100 g⁻¹.min⁻¹, mean +/- SEM, p less than 0.01; 49.6 +/- 2.0, p less than 0.005; 53.4 +/- 3.0, p less than 0.01, at 1, 2, and 4 h PA, respectively, versus 85.7 +/- 6.9 at control, whereas both the hyper- and hypoglycemic groups did not differ significantly from control measurements. Cerebral oxygen consumption (CMRO₂) was significantly decreased in all three groups 5 min PA and remained decreased in the late period after asphyxia in both the unregulated and hypoglycemic groups. In the unregulated group, CMRO₂ was 191 +/- 14 microM.100 g⁻¹.min⁻¹, mean +/- SEM, p less than 0.05; 200 +/- 4; and 181 +/- 10, p less than 0.05 at 1, 2, and 4 h, respectively, PA versus 251 +/- 12 at control..

Comments: Animal study with glucose pretreatment; did not look at overall neurologic or pathologic outcomes but suggests that hyperglycemia normalizes cerebral metabolism post-asphyxia.

Level of Evidence 6

Quality Good

Evidence - Supportive

J. Y. Yager, D. F. Heitjan, J. Towfighi, and R. C. Vannucci. Effect of insulin-induced and fasting hypoglycemia on perinatal hypoxic-ischemic brain damage. *Pediatr.Res.* 31:138-142,

1992.

Experiments in adult animals have indicated that hyperglycemia accentuates whereas hypoglycemia ameliorates hypoxic-ischemic brain damage. To determine whether hypoglycemia is protective or deleterious to the perinatal brain subjected to hypoxia-ischemia, 7-d postnatal rats were rendered hypoglycemic either by receiving an s.c. injection of insulin or fasting for 12 h. All rat pups underwent unilateral common carotid artery ligation followed by exposure to 8% oxygen-balance nitrogen at 37 degrees C for 2 h. Control animals (no insulin or fasting) received s.c. injections of normal saline. Mean blood glucose concentrations were 5.4 +/- 0.1, 4.3 +/- 0.2, and 3.4 +/- 0.1 mmol/L for control, insulin, and fasted animals, respectively. Blood beta-hydroxybutyrate concentrations were identical (0.5 +/- 0.1 mmol/L) for control and insulin-treated animals, but more than doubled in concentration in the fasted animals (p less than 0.001). Mortality rates during hypoxia-ischemia were higher in the insulin-treated animals (30%) than in either the fasted (4%) or control (0%) animals (p less than 0.05). Fasted animals showed a significant reduction in hypoxic-ischemic brain damage as compared with either the insulin-treated or control animals. Insulin-treated animals were not significantly different from controls. The findings indicate that 1) insulin induced hypoglycemia does not provide a protective effect on perinatal hypoxic-ischemic brain damage, as in adults; and 2) fasting adequate to produce hypoglycemia and ketonemia improved neuropathologic outcome.

Comments: Animal study with pre-insult manipulation of glucose, but actual blood glucose concentration not specifically regulated. Results suggests that hyperinsulinemic hypoglycemia (as may occur post-asphyxia) increases injury due to suppression of ketone production.

Level of Evidence 6

Quality Good

Evidence - Supportive

A. R. Laptook, R. J. T. Corbett, O. Arencibia-Mireles, and J. Ruley. Glucose-associated alterations in ischemic brain metabolism of neonatal piglets. *Stroke* 23:1504-1511, 1992. **BACKGROUND AND PURPOSE:** During global brain ischemia or hypoxia-ischemia in adults, hyperglycemia is deleterious to the brain. In contrast, similar adverse effects have not been found in neonatal animals. This investigation examined neonatal piglets to determine if there were specific alterations of ischemic brain metabolism associated with different systemic glucose concentrations and to potentially clarify the effects of hyperglycemia during ischemia in neonates. **METHODS:** Two groups of animals (n = 12 in each group) were studied during partial ischemia to compare the effects of hyperglycemia (plasma glucose concentration, 258 +/- 97 mg% [mean +/- SD]) with modest hypoglycemia (plasma glucose concentration, 62 +/- 23 mg%). A broad spectrum of cerebral blood flow reduction was achieved by combining inflation of a cervical pressure cuff with varying degrees of hemorrhagic hypotension. High-energy phosphorylated metabolites, intracellular pH, and cerebral blood flow were simultaneously measured using a magnetic resonance spectroscopic technique. Brain metabolic variables (beta-ATP, inorganic phosphorus, phosphocreatine, intracellular pH) were plotted as a function of blood flow reduction during partial ischemia

for each group. RESULTS: During ischemia values of cerebral blood flow were comparably distributed between groups and ranged from 15% to 110% of those of control. At a given reduction of cerebral blood flow, hyperglycemic piglets maintained a higher concentration of beta-ATP ($p = 0.011$) and had a smaller increase in inorganic phosphorus (p less than 0.001). At cerebral blood flow less than 50% of control, the intracellular pH of piglets with modest hypoglycemia during partial ischemia was never reduced to less than 6.46, whereas intracellular pH fell as low as 5.97 for hyperglycemic animals. CONCLUSIONS: ATP preservation may account for the differing effects of glucose during ischemia in neonates compared with adults, provided that the accentuated brain acidosis is not deleterious to neonatal brain tissue.

Comment: Animal study with pre-insult manipulation of glucose; hypoglycemia during partial ischemia associated with depletion of ATP and PCr in brain. Piglet model may be better than rodent models as the piglet brain is dependent on glucose while neonatal rat brain relies on fat as primary energy source for the first 7-10 days of postnatal life.

Level of Evidence 6
Quality Good
Evidence - Supportive

R. A. Sheldon, J. C. Partridge, and D. M. Ferriero. Postischemic hyperglycemia is not protective to the neonatal rat brain. *Pediatr.Res.* 32:489-493, 1992.
Brain glucose concentration during and after hypoxia-ischemia may be one of the variables affecting outcome of asphyxial insults. Glucose given before global ischemic forebrain injury to adult rats increases morphologic brain damage, and postischemic insulin administration reduces selective neuronal necrosis and cortical infarction. Because glucose infusions are routinely used in the clinical management of perinatal asphyxia, we evaluated the role of glucose administration after ischemic neuronal damage to neonatal rat brain. Sprague-Dawley rat pups (postnatal d 7) were subjected to left common carotid artery ligation followed by 2.5 h of 8% oxygen (Levine procedure). The experimental group was subdivided so that pups received either systemic injections of glucose or saline immediately after the hypoxic insult. Animals were killed on postnatal d 12 and brain areas of ipsi- and contralateral cortex and caudate were calculated from camera lucida tracings. There was no significant difference in size of brain infarction between postischemic glucose-treated and post-ischemic saline-treated pups. However, hypoxic-ischemic brains did show more severe neuronal damage when hyperglycemia was induced after asphyxia. Because post-ischemic hyperglycemia does not attenuate and may exacerbate injury, we recommend careful monitoring of blood glucose so that hyperglycemia does not occur during resuscitation of asphyxiated infants.

Comment: Glucose treatment post-insult; no regulation of glucose concentration. Contradicts Hattori and Wasterlain, with suggestion that there may be an increase in neuronal injury after glucose administration.

Level of Evidence 6

Quality * Good
Evidence - * Supportive

M. H. LeBlanc, M. Huang, V. Vig, D. Patel, and E. E. Smith. Glucose affects the severity of hypoxic-ischemic brain injury in newborn pigs. *Stroke* 24:1055-1062, 1993.

BACKGROUND AND PURPOSE: The administration of glucose has been shown to worsen brain injury in adult animals but has no effect on the severity of injury in newborn rats. We wished to see whether the results in newborn rats could be extended to another newborn animal. **METHODS:** In 44 0- to 3-day-old piglets, hypoxic-ischemic central nervous system damage was induced by ligation of both carotid arteries and reduction of their blood pressure to two-thirds normal for one-half hour. In the last 15 minutes of this half hour, oxygen concentration was reduced to 6%. The piglets were randomized to receive either 2 mL/kg 50% dextrose in water followed by 2 mL/kg per hour for 2.5 hours beginning before ischemia or enough insulin to reduce their resting blood sugar to approximately 2 mmol/L. **RESULTS:** Neurological exam scores in the glucose-treated piglets at 1 day after injury were significantly worse than those in the insulin-treated group. Pathological examination scores were poorer in the glucose-treated group (13.6 +/- 1.9 [mean +/- SEM]) than in the insulin-treated group (24.7 +/- 1.4, P < .01). **CONCLUSIONS:** Increasing serum glucose during hypoxic-ischemic injury to the newborn piglet's brain worsens brain injury.

Comments: Animal study with pre-insult manipulation of glucose; no target glucose level identified for hyperglycemia animals.

Level of Evidence 6

Quality Good

Evidence - Supportive

Tuor, U. I., C. S. Simone, et al. (1993). Glucocorticoid prevention of neonatal hypoxic-ischemic damage: role of hyperglycemia and antioxidant enzymes. *Brain Res* 604(1-2): 165-72.

Recently, we observed that pre-treatment of neonatal rats with dexamethasone prevents brain damage associated with cerebral hypoxia-ischemia (unilateral carotid occlusion + 3 h hypoxia). Presently, we investigate whether hyperglycemia or an induction of endogenous free radical scavengers explains dexamethasone's neuroprotective effect. Pathological damage was examined in rats maintained hyperglycemic during hypoxia-ischemia by the repeated administration of 10% glucose (10 ml/kg, i.p.) at 0, 1, 2 and 3 h of hypoxia (n = 14) and this damage was compared to that in control (n = 15) or dexamethasone (0.1 mg/kg, i.p., n = 15) treated animals. Despite similar elevations in blood glucose at the end of hypoxia, glucose treated animals had greater damage than dexamethasone treated animals and both of these groups had less damage than controls (volumes of damage of approx. 30.9 +/- 10, 3.4 +/- 2.3 and 60.4 +/- 7.1% of the hemisphere, respectively; P < 0.0001). Anti-oxidant enzyme activities were measured within brains of animals treated with dexamethasone or vehicle (n = 44). Activities of the enzymes catalase, glutathione peroxidase and CuZn- or Mn-superoxide dismutase were similar in both treatment groups, with or without exposure to hypoxia-ischemia. Thus, an induction of antioxidant enzymes does not explain dexamethasone's

effects whereas the relative hyperglycemia associated with glucocorticoid treatment may contribute partially. Neither account fully for dexamethasone's protective effect suggesting an additional glucocorticoid mediated mechanism must be involved.

Comments: Animal study with glucose administration before and during insult. Not designed to examine the effect of glucose on hypoxic-ischemic brain injury, but did show partial protective effect of hyperglycemia.

Level of Evidence 7

Quality Good

Evidence - Supportive

Laptook, A. R., R. J. Corbett, et al. (1994). The effects of systemic glucose concentration on brain metabolism following repeated brain ischemia. *Brain Res* 638(1-2): 78-84.

Since systemic glucose concentration is an important determinant of ischemic brain metabolism in neonates, we sought to determine if the systemic glucose concentration influences brain metabolic alterations following repeated partial ischemia. A group of hyperglycemic piglets (n = 12) were compared to a group of modestly hypoglycemic piglets (n = 12) using in vivo ²H and ³¹P magnetic resonance spectroscopy to simultaneously measure cerebral blood flow and phosphorylated metabolites before, during and 30 min after two 10-min episodes of ischemia (i.e. Recovery 1 and 2). For both groups, beta-ATP levels at Recovery 1 and 2 were lower than Control (91 +/- 11 and 83 +/- 15% of Control, respectively for both groups combined, P = 0.002 vs Control). Inorganic phosphorus was elevated in hyperglycemic piglets at Recovery 1 and 2 (117 +/- 15 and 118 +/- 10% of Control). In contrast, in modestly hypoglycemic piglets inorganic phosphorus progressively rose from Recovery 1 (131 +/- 24% of Control) to Recovery 2 (149 +/- 37% of Control), and differed from the hyperglycemic group (P = 0.02). These changes did not correlate with post-ischemic cerebral blood flow, cerebral O₂ delivery or cerebral glucose delivery. In both groups phosphocreatine and intracellular pH returned to Control values during Recovery 1 and 2. The progressive increase in inorganic phosphorus post-ischemia in hypoglycemic piglets suggests that modest hypoglycemia during and following repeated partial ischemia adversely affects immediate brain metabolic recovery.

Comments: Animal study with pre-insult manipulation of glucose; did not examine neurologic or pathologic outcomes but found deleterious effect of hypoglycemia on post-ischemic brain metabolism.

Level of Evidence 7

Quality Good

Evidence - Supportive

M. H. LeBlanc, M. Huang, D. Patel, E. E. Smith, and M. Devidas. Glucose given after hypoxic ischemia does not affect brain injury in piglets. *Stroke* 25 (7):1443-1447, 1994.
BACKGROUND AND PURPOSE: Giving glucose before hypoxic ischemia worsens brain

injury in piglets. Does giving glucose after hypoxic ischemia affect severity of injury?
METHODS: Forty-three 0- to 3-day-old pigs were used. All piglets received 2 U/kg insulin before injury to prevent stress-induced hyperglycemia. Hypoxic ischemic brain damage was induced by clamping both carotid arteries and reducing arterial blood pressure to two thirds of normal by hemorrhage at time 0. At 15 minutes the fraction of inspired oxygen (FIO₂) was reduced to 6%. At 30 minutes FIO₂ was increased to 100%, the carotids were released, and the withdrawn blood was reinfused. The piglets were then randomized to receive either 2 mL/kg of 50% dextrose followed by 2 mL/kg per hour for 2 hours or an equal volume of saline. RESULTS: Neurological examination scores (20 is normal, 5 is brain dead, by blinded observer) at 1 day postinjury were similar in the two groups: glucose, median 15.5 (25th percentile, 12.2; 75th percentile, 18); controls, 15.6 (9.3, 18). Piglets were killed at 3 days with brain preservation at death. Pathological examination scores (sum of scores from cortex, hippocampus, and basal ganglia: 30 is normal, 3 is total necrosis) by blinded observer were similar in the two groups: glucose, 26 (18, 28); controls, 25 (16.5, 28); NS. CONCLUSIONS: Although elevated glucose levels during hypoxic ischemic injury worsen brain injury in the piglet, elevated glucose levels after injury do not affect the severity of the injury.

Comments: Animal study with post-insult manipulation of glucose; glucose concentration not specifically controlled. Found no effect of glucose administration on hypoxia-ischemic brain injury.

Level of Evidence 7

Quality Good

Evidence – Neutral to opposing

J. E. McGowan, P. J. Marro, O. P. Mishra, and M. Delivoria-Papadopoulos. Brain cell membrane function during hypoxia in hyperglycemic newborn piglets. *Pediatr.Res.* 37:133-139, 1995.

To test the hypothesis that acute hyperglycemia reduces changes in cell membrane structure and function during cerebral hypoxia in the newborn, brain cell membrane Na⁺,K⁽⁺⁾-ATPase activity and levels of membrane lipid peroxidation products were measured in four groups of anesthetized, ventilated newborn piglets: normoglycemia/normoxia (control, group 1, n = 12), hyperglycemia/normoxia (group 2, n = 6), untreated hypoxia (group 3, n = 10), and hyperglycemia/hypoxia (group 4, n = 7). Hyperglycemia (blood glucose concentration 20 mmol/L) was induced using the glucose clamp technique. The hyperglycemic glucose clamp was maintained for 90 min before onset of hypoxia and throughout the period of hypoxia. Cerebral tissue hypoxia was induced in groups 3 and 4 by reducing fraction of inspired oxygen for 60 min and was documented by a decrease in the ratio of phosphocreatine to inorganic phosphate as measured using ³¹P-nuclear magnetic resonance spectroscopy. Blood glucose concentration during hypoxia in hyperglycemic hypoxic animals was 20.7 +/- 1.2 mmol/L, compared with 10.3 +/- 1.7 mmol/L in untreated hypoxic piglets (p < 0.05). Peak blood lactate concentrations were not significantly different between the two hypoxic groups (8.4 +/- 2.8 mmol/L versus 7.8 +/- 1.6 mmol/L). In cerebral cortical membranes prepared from the untreated animals, cerebral tissue hypoxia caused a 25% reduction in Na⁺,K⁽⁺⁾-

ATPase activity compared with normoxic controls and an increase in conjugated dienes and fluorescent compounds, markers of lipid peroxidation. In contrast, Na⁺,K⁽⁺⁾-ATPase activity and levels of lipid peroxidation products in hyperglycemic hypoxic animals were not significantly different from the values in control normoxic animals.(ABSTRACT TRUNCATED AT 250 WORDS)

Comments: Animal study with glucose pretreatment and controlled glucose concentration; pure hypoxia rather than hypoxia-ischemia; only looked at biochemical indices of injury, not neurologic or pathologic outcomes.

Level of Evidence 7

Quality Good

Evidence - Supportive

T. S. Park, E. R. Gonzales, A. R. Shah, and J. M. Gidday. Hypoglycemia selectively abolishes hypoxic reactivity of pial arterioles in piglets: role of adenosine. *Am.J Physiol* 268 (2 Pt 2):H871-H878, 1995.

Episodes of hypoxia often occur in hypoglycemic newborns, but it is not known whether dysfunctions in cerebrovascular regulation contribute to brain injury incurred by these affected neonates. We tested the hypotheses that 1) perinatal hypoglycemia impairs cerebrovascular responses to hypoxia and 2) a reduced vascular smooth muscle sensitivity to adenosine accounts for this impairment. Responses of 25- to 50- μ m-diam pial arterioles were determined using the cranial window technique in isoflurane-anesthetized newborn piglets < 5 days of age. Hypoxia (arterial PO₂ = 28 \pm 1 mmHg) caused a 47 \pm 5% increase (P = 0.0008) in arteriolar diameter, 89% of which could be blocked by prior superfusion of the window space with the preferential A₂-adenosine receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX; 50 μ M). Insulin-induced hypoglycemia (blood glucose = 18 \pm 1 mg/dl without isoelectric electroencephalogram) caused a 31 \pm 5% increase (P = 0.002) in arteriolar diameter; however, no additional dilatative response to hypoxia (arterial PO₂ = 28 \pm 1 mmHg) could be elicited in these animals. Arteriolar dilation of 41 \pm 6% (P = 0.002) induced by superfusion of 20 μ M adenosine under normoglycemic conditions was also completely abolished after the animals were rendered hypoglycemic. Unlike the response to hypoxia and adenosine, hypoglycemia only attenuated prostanoid-dependent dilations to hypercapnia (arterial PCO₂ = 68 \pm 3 mmHg) by 55 \pm 9%. These results indicate that, in the newborn, hypoglycemia selectively abolishes hypoxic reactivity through an impairment in adenosine-mediated cerebrovascular dilatation.

Comments: Animal study with pre-hypoxic manipulation of glucose; did not look at long-term outcomes. Results suggest that hypoglycemia could exacerbate hypoxic injury by blunting normal physiologic responses.

Level of Evidence 6

Quality * Good

Evidence - * Opposing

Y. Lin and G. Greisen. Analysis of the risk of brain damage in asphyxiated infants. *J*

Perinat.Med. 24 (6):581-589, 1996.

The objectives of this study were to analyze the influence of maternal, perinatal and neonatal factors on the neurological sequelae occurring in asphyxiated infants. The clinical records of 79 infants, 35 weeks of gestation or more, treated in the neonatal intensive care unit in whom the principal diagnosis was asphyxia, and who had no major malformation and who survived for more than 24 hours, were analyzed. Analysis of variance was used to compare neurological outcome classified as 1) normal development or mild neurological sequelae, 2) moderate to severe neurological sequelae, and 3) withdrawal of treatment because of signs and symptoms of severe brain damage. The group in whom treatment was withdrawn had lower mean arterial blood pressure on admission, blood glucose and plasma sodium levels than those in the moderate to severe handicap group. The combined group of brain damaged infants, (2 + 3), had lower Apgar scores at five minutes, umbilical cord arterial blood Standardized Base Excess (SBE), lower urinary output, and higher incidence of seizures and higher plasma potassium level than the group with normal development or those with mild handicap. Stepwise multiple logistic regression confirmed these.

Comments: Retrospective chart review; analysis of variance found association of lower blood glucose concentrations and early severe neurologic impairment.

Level of Evidence *

Quality * Fair

Evidence - * Supportive

R. C. Vannucci, A. Rossini, and J. Towfighi. Effect of hyperglycemia on ischemic brain damage during hypothermic circulatory arrest in newborn dogs. *Pediatr.Res.* 40 (2):177-184, 1996. The effect of hyperglycemia on ischemic brain damage was investigated in a newborn dog model of hypothermic circulatory arrest. Newborn dogs were anesthetized with halothane, paralyzed, and artificially ventilated to maintain normoxia and acid-base balance. Animals were surface-cooled to 20 degrees C, after which cardiac arrest was effected with i.v. KCl. Before surface cooling, one-half of the dogs (n = 12) received a bolus injection of 50% glucose to increase plasma glucose concentrations to approximately 33 mmol/L (600 mg/dL); control littermates (n = 12) received an equivalent volume of 1 N saline. The dogs remained asystolic for 1.75 h, after which cardiopulmonary resuscitation was accomplished. All animals survived, were allowed to recover from anesthesia at 37 degrees C, and were maintained for 8 h of recovery, at which interval they underwent perfusion-fixation of their brains for pathologic analysis. Histologic grading of brain damage showed no statistically significant difference in the severity of neuronal necrosis within the cerebral cortex or caudate nucleus between hyperglycemic and normoglycemic littermates, with greater brain damage apparent in the amygdaloid nucleus of the hyperglycemic dogs (p < 0.02). Brainstem injury occurred more frequently in the hyperglycemic animals (p < 0.05). Correlation of coefficients analyses revealed a positive correlation between the severity of brain damage and plasma glucose concentration for both the caudate nucleus and amygdaloid nucleus but not for the cerebral cortex. The findings suggest that hyperglycemia superimposed upon hypothermic circulatory arrest in the newborn dog accentuates brain damage only in selected regions of the brain, especially the caudate and amygdaloid nuclei and brainstem, excluding the cerebral cortex.

Comments: Animal study with pre-insult glucose administration and specific extremely hyperglycemic (6x normal) target glucose level; did not use standard hypoxic-ischemic model. Hyperglycemia increased injury only in specific subcortical structures, not cerebral cortex; extreme degree of hyperglycemia make it difficult to extrapolate results to usual clinical setting.

Level of Evidence 6

Quality * Good

Evidence - * Opposing

M. H. LeBlanc, X. B. Qian, and Z. W. Cai. The effect of glucose during ischemia on brain ATP, lactate, and glutamate in piglets. *Biol. Neonate* 72 (4):243-254, 1997.

Glucose worsens hypoxic-ischemic brain injury in 0- to 3-day-old piglets. Piglets were randomly assigned to have blood glucose increased with glucose infusion (n = 12), or decreased with insulin (n = 13), or a sham group (n = 10). In the insulin and glucose groups at time 0, both carotid arteries were clamped, and blood was withdrawn to reduce the blood pressure one third. At time 15 min FiO₂ was reduced to 6%. At time 30 min cerebrospinal fluid (CSF) was taken for glutamate, and the brains were frozen. The shams had CSF removed and brains frozen without hypoxia or ischemia. Brain ATP was 1.7 +/- 0.09 mumol/g wet weight in the shams, 0.98 +/- 0.09 in the glucose group (p < 0.01 vs. sham), and 0.52 +/- 0.10 in the insulin group (p < 0.01 vs. glucose). Brain lactate levels were 4.3 +/- 1.0 mumol/g wet weight in the shams, 18.3 +/- 1.9 in the insulin group (p < 0.01 vs. sham), and 29.4 +/- 2.6 in the glucose group (p < 0.01 vs. insulin). CSF glutamate was 9.3 +/- 3.6 microM in the glucose group, 9.6 +/- 3.5 in the insulin group, and 2.2 +/- 0.9 in the shams (p < 0.05, glucose and insulin > sham). The B_{max} for MK-801 binding was 2.3 +/- 0.2 pmol/mg protein in the glucose group, 2.6 +/- 0.1 in the insulin group (p < 0.05 vs. sham), and 2.0 +/- 0.2 in the shams, and the K_d was the same in the three groups (p = nonsignificant). Brain Na⁺,K⁽⁺⁾-ATPase was the same in the three groups (p = nonsignificant). Providing additional glucose preserves ATP during hypoxic-ischemic brain injury in the piglet but does not change CSF glutamate or brain MK-801 binding and probably worsens outcome by elevating brain lactate levels above the threshold for cellular injury.

Comments: Animal study with pre-insult manipulation of glucose; did not look at neurologic or pathologic outcomes. Conclusion that hyperglycemia may worsen outcome because of effects on lactate levels not supported by data, merely speculative.

Level of Evidence 6

Quality * Good

Evidence - * Opposing

A. M. Brambrink, R. N. Ichord, L. J. Martin, R. C. Koehler, and R. J. Traystman. Poor outcome after hypoxia-ischemia in newborns is associated with physiological abnormalities during early recovery. Possible relevance to secondary brain injury after head trauma in infants. *Exp. Toxicol. Pathol.* 51 (2):151-162, 1999.

"Secondary hypoxia/ischemia" (i.e. regional impairment of oxygen and substrate delivery) results in secondary deterioration after traumatic brain injury in adults as well as in children and infants. However, detailed analysis regarding critical physiological abnormalities

resulting from hypoxia/ischemia in the immature brain, e.g. acid-base-status, serum glucose levels and brain temperature, and their influence on outcome, are only available from non-traumatic experimental models. In recent studies on hypoxic/asphyxic cardiac arrest in neonatal piglets, we were able to predict short-term outcome using specific physiologic abnormalities immediately after the insult. Severe acidosis, low serum glucose levels and fever after resuscitation were associated with an adverse neurologic recovery one day after the insult. The occurrence of clinically apparent seizure activity during later recovery increased mortality (epileptic state), and survivors had greater neocortical and striatal brain damage. Brain damage after transient hypoxia/ischemia and "secondary brain injury" after head trauma may have some mechanistic overlap, and these findings on physiological predictors of outcome may also apply to pathologic conditions in the post-traumatic immature brain. Evaluation of data from other models of brain injury will be important to develop candidate treatment strategies for head-injured infants and children and may help to initiate specific studies about the possible role of these physiological predictors of brain damage in the traumatically injured immature brain.

Comments: Retrospective analysis of data from animal study that was specifically designed to look at effects of glucose concentration. Low blood glucose levels associated with poor short-term neurologic outcomes, but glucose concentrations were not specifically regulated.

Level of Evidence 6

Quality Fair

Evidence - Supportive

Y. S. Chang, W. S. Park, S. Y. Ko, M. J. Kang, J. M. Han, M. Lee, and J. Choi. Effects of fasting and insulin-induced hypoglycemia on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. *Brain Res.* 844 (1-2):135-142, 1999.

This study was done to determine the effects of 12 h fasting-induced mild hypoglycemia (blood glucose 60 mg/dl) and insulin-induced moderate hypoglycemia (blood glucose 35 mg/dl) on brain cell membrane function and energy metabolism during hypoxia-ischemia in newborn piglets. Sixty-three ventilated piglets were divided into six groups; normoglycemic control (NC, n=8), fasting-induced mildly hypoglycemic control (FC, n=10), insulin-induced moderately hypoglycemic control (IC, n=10), normoglycemic/hypoxic-ischemic (NH, n=11), fasting-induced mildly hypoglycemic/hypoxic-ischemic (FH, n=12) and insulin-induced moderately hypoglycemic/hypoxic-ischemic (IH, n=12) group. Cerebral hypoxia-ischemia was induced by occlusion of bilateral common carotid arteries and simultaneous breathing with 8% oxygen for 30 min. The brain lactate level was elevated in NH group and this change was attenuated in FH and IH groups. The extent of cerebral lactic acidosis during hypoxic-ischemic insult showed significant positive correlation with blood glucose level ($r=0.55$, $p<0.001$). Cerebral Na⁺, K⁺-ATPase activity and concentrations of high-energy phosphate compounds were reduced in NH group and these changes were not ameliorated in FH or IH group. Cortical levels of conjugated dienes, measured as an index of lipid peroxidation of brain cell membrane, were significantly elevated in NH, FH and IH groups compared with NC, FC and IC groups and these increases were more profound in FH and IH

with respect to NH. Blood glucose concentration showed significant inverse correlation with levels of conjugated dienes ($r=-0.35$, $p<0.05$). These findings suggest that, unlike in adults, mild or moderate hypoglycemia, regardless of methods of induction such as fasting or insulin-induced, during cerebral hypoxia-ischemia is not beneficial and may even be harmful in neonates.

Comments: Animal study with pre-insult manipulation of glucose; did not consider neurologic or pathologic outcome, only biochemical indices of altered brain structure. Indices altered more with hypoglycemia than normoglycemia.

Level of Evidence 6

Quality Fair

Evidence - Supportive

W. S. Park, Y. S. Chang, and M. Lee. Effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after acute transient global hypoxia-ischemia in the newborn piglet. *Brain Res.* 901 (1-2):102-108, 2001.

This study was done to determine the effects of hyperglycemia or hypoglycemia on brain cell membrane function and energy metabolism during the immediate reoxygenation-reperfusion period after hypoxia-ischemia (HI). Forty-five newborn piglets were divided randomly into four experimental groups: normoxia control (NC, n=9); HI/reoxygenation-reperfusion (RR) control (HC, n=11); HI/RR hyperglycemia (HE, n=12); and HI/RR hypoglycemia (HO, n=13) group. Animals were subjected to transient HI for 30 min followed by 2 h of RR. Cerebral HI was induced by temporary but complete occlusion of bilateral common carotid arteries with surgical clips and simultaneous breathing with 8% oxygen. Glucose was unregulated in HC group, and controlled by modified glucose clamp technique immediately after HI in HE (350 mg/dl) and HO (50 mg/dl) groups. During HI, heart rate, base deficit, glucose and lactate level in the blood and cerebrospinal fluid increased, and arterial pH, oxygen saturation and blood pressure decreased significantly in HC, HE and HO groups. During RR, these abnormalities returned to normal values, but lactic acidosis persisted especially in HO group. Cerebral Na(+),K(+)-ATPase activity decreased, and lipid peroxidation products increased significantly in HC group than in NC group, and these abnormalities were significantly aggravated in HE, but not in HO, group. Brain ATP and phosphocreatine levels in HE group were significantly reduced compared to the corresponding values in NC, HC and HO groups. In summary, hyperglycemia, but not hypoglycemia immediately after HI interfered with the recovery of brain cell membrane function and energy metabolism. These findings suggest that post-hypoxic-ischemic hyperglycemia is not beneficial and might even be harmful in neonatal hypoxic-ischemic encephalopathy.

Comments: *Animal study with post-insult manipulation of glucose and specific target glucose concentrations; measured biochemical indices of altered brain structure and metabolism, not neurologic or pathologic outcomes. Found deleterious effect of hyperglycemia but not hypoglycemia.*