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Intraoperative Hyperglycemia during Infant Cardiac Surgery Is Not Associated with Adverse Neurodevelopmental Outcomes at 1, 4, and 8 Years

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Background: **It is unknown whether intraoperative hyperglycemia in infants is associated with worse neurodevelopmental outcomes after low-flow cardiopulmonary bypass (LF), deep hypothermic circulatory arrest (CA), or both.**

Methods: **In a database review of a prospective trial of 171 infants undergoing arterial switch for D-transposition of the great arteries who were randomly assigned to predominately LF or CA, glucose was measured after induction (T1), 5 min after cardiopulmonary bypass onset (T2), at the onset of CA or LF (T3), 5 min after CPB resumption (T4), at rewarming to 32°C (T5), 10 min after cardiopulmonary bypass weaning (T6), and 90 min after CA or LF (T7). Outcomes included seizures, electroencephalographic findings, and neurodevelopmental evaluation at 1, 4, and 8 yr.**

Results: **Glucose concentrations were affected by support strategy and age at surgery. Lower glucose in the entire group at T6–T7 tended to predict electroencephalographic seizures ($P = 0.06$ and $P = 0.007$) but was not related to clinical seizures. Within the predominantly CA group, higher glucose did not correlate with worse outcomes. Rather, it was associated with more rapid electroencephalographic normalization of "close burst" and "relative continuous" activity at all times except T2 ($P \leq 0.03$), a finding more pronounced in infants aged 7 days old or younger. Intraoperative serum glucose concentrations were unrelated to neurodevelopmental outcomes at ages 1, 4, and 8 yr.**

Conclusions: **Low glucose after cardiopulmonary bypass tended to relate to electroencephalographic seizures and slower electroencephalogram recovery, independent of CA duration. High glucose concentrations were not associated with worse neurodevelopmental outcomes. Avoiding hypoglycemia may be preferable to restricting glucose in infants undergoing heart surgery.**

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NEUROLOGIC outcome after neonatal and infant heart surgery using deep hypothermic cardiopulmonary bypass (CPB) techniques may be influenced by a number of factors, including preoperative condition, duration of CPB, duration of circulatory arrest, the rate and depth of cooling, perfusion flow rates, hematocrit, and blood gas management during deep hypothermia.[1–3] The influence of serum glucose concentrations during and after CPB on early and longer-term neurologic and developmental outcomes has not been studied prospectively.

Glucose infusions are usually avoided in adults undergoing cardiac surgery.[4] Increased glucose concentrations in adults who have experienced cardiac arrest[4] and traumatic head injury[5] have been associated with worse neurologic outcome. Animal models have also shown that glucose worsens outcomes from both global and focal ischemia,[6] and they support the adverse effect of hyperglycemia in normothermic arrest as measured by standardized neurologic scoring and cerebral pathology.[7,8]

The effect of glucose on neurologic outcome after an ischemic injury may be different in pediatric patients. A small retrospective study of pediatric patients who underwent cardiac surgery suggested a tendency toward worse neurologic outcome with high glucose concentrations, but statistical significance was not achieved.[9] In contrast, immature animal studies have shown that an increased glucose concentration may ameliorate some neurologic injury associated with bypass and ischemia,[10] and magnetic resonance imaging (MRI) spectroscopy of intracellular pH and high energy phosphates have indicated that hyperglycemia does not have an adverse effect on neurologic recovery after ischemia.[11,12]

We reviewed an existing prospectively collected database with short- and long-term follow-up of infants who had undergone an arterial switch operation for D-transposition of the great arteries to investigate whether perioperative glucose concentrations were associated with adverse neurologic and developmental outcomes.

Materials and Methods

The Boston Circulatory Arrest Study was a single-center, prospective, randomized trial of 171 infants who

underwent an arterial switch operation for D-transposition of the great arteries with either an intact ventricular septum or a ventricular septal defect at Children's Hospital, Boston, Massachusetts, between April 1988 and February 1992, and received either low-flow CPB (LF) or deep hypothermic cardiac arrest (CA). Study design, enrollment criteria, consent procedure, and patient sample have been previously described in detail and were approved by the Children's Hospital Institutional Review Board.[1] Summarizing the protocol, patients were randomly assigned to a CPB strategy of either predominant CA or predominant LF (50 ml/kg), with stratification according to diagnosis and surgeon; all patients had a variable period of CA to close atrial or ventricular septal defects. Anesthesia and perfusion monitoring techniques were tightly standardized and have also been described elsewhere.[1] Anesthesia was induced with 50 μg/kg fentanyl along with 100 μg/kg pancuronium, and surface cooling was instituted with a low ambient room temperature, a cooling mattress, and ice packs to the head; the mean ($\pm$ SD) tympanic membrane temperature at the onset of bypass was 32.7 $\pm$ 1.3°C. Additional doses of fentanyl and pancuronium (25 and 100 μg/kg, respectively) were given after CPB initiation, along with thiopental when the tympanic temperature reached 18°C. The tympanic membrane temperature was maintained at 18°C or less during the period of LF or CA and was maintained constant from the start of LF or CA through to the start of rewarming. Patients were given 10–20 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution intraoperatively; supplemental glucose was given for blood concentrations less than 50 mg/dl (2.8 mM). Otherwise, no maintenance glucose was given. All patients received 30 mg/kg methylprednisolone at the onset of CPB. During the period in which this study was conducted, a CPB strategy of α-stat monitoring and relatively low hematocrit (approximately 20%) was used.

Laboratory Measurements

Glucose concentrations were measured at seven perioperative time points: after induction of anesthesia before surgical incision (T1), 5 min after bypass initiation (T2), with onset of either CA or LF (T3), 5 min after resumption of bypass and the start of rewarming (T4), during rewarming at rectal temperature of 32°C (T5), 10 min after weaning from bypass (T6), and 90 min after the end of CA or LF (T7). The normal glucose range for our laboratory is 60–115 mg/dl (3.3–6.4 mM). When the infants were originally enrolled in this study, those with a glucose concentration less than 50 mg/dl (2.8 mM) were treated for hypoglycemia, and we therefore maintained this as the lower glucose concentration for analysis. Because we were not attempting to relate a specific glucose concentration with adverse neurodevelopmental outcome, we defined a range of glucose that may be clinically relevant and chose an upper concentration greater than 150 mg/dl (8.3 mM) for analysis purposes.

Short-term Neurologic Outcomes

Clinical examination was performed by a neurologist who was blinded to support strategy and glucose concentration. Patients were examined both preoperatively and 7–10 days postoperatively, or before discharge. Fifteen-channel electroencephalographic monitoring was performed continuously from 2 h preoperatively to 48 h postoperatively and was then repeated before discharge. The reappearance of electroencephalographic latency was recorded, as well as the time to "close bursts," "relative continuous" electroencephalographic activity, "continuous pattern" electroencephalogram, and the occurrence of electroencephalographic seizure activity (defined as rhythmic paroxysmal activity $>$ 5 s).[1] Recovery of *close bursts* is designated as the time when there is an interval of less than 15 s between bursts of electroencephalographic activity. *Relative continuous activity* occurs when, in a span of 60 s, the longest interval between electroencephalographic activity is 6 s. *Continuous pattern* is designated as the finding that the longest interval between electroencephalographic activity is less than 1 s. Although these indices of electroencephalogram recovery are nonspecific and are not related to a particular predictive outcome variable, Newburger *et al.*,[1] reporting the early postoperative outcomes for this cohort of patients, described a relation between delayed recovery of electroencephalographic activity and subsequent encephalographic seizure activity in infants with D-transposition of the great arteries and intact ventricular septum who were assigned to the predominant CA strategy. Electroencephalograms were interpreted by one of four pediatric epileptologists blinded to support strategy and were reviewed at a weekly conference to achieve consensus. Potential adverse acute neurologic outcomes were defined as longer time to electroencephalogram recovery.

Long-term Neurologic and Developmental Outcomes

Neurodevelopmental evaluations were performed at 1, 4, and 8 yr; the methodology has previously been described.[13–15] Patients who returned for follow-up at 1 yr underwent testing using the Bayley Scales, which include the Psychomotor Developmental Index and the Mental Developmental Index, the Fagan Test of Infant Intelligence, a neurologic examination, and a brain MRI. Parental intelligence was evaluated using the Revised Peabody Picture Vocabulary Test. At the age of 4 yr, Full-scale, Verbal, and Performance intelligence quotients were evaluated using the Revised Wechsler Preschool and Primary Scale of Intelligence, along with gross and fine motor skills using the Peabody Developmental Motor Scales and the Grooved Pegboard, auditory

comprehension of language, and structural and functional oral and speech motor control. At 8 yr, intelligence quotient was again tested using the Wechsler Intelligence Test for Children–Third Edition, along with math and reading using the Wechsler Individual Achievement Test. Sociodemographic and health information was collected at each follow-up. Abnormal developmental outcomes were defined according to each assessment tool as deviating from normative data. Findings on neurologic examination at each assessment were classified as normal, possibly abnormal, or definitely abnormal. Definite abnormalities were subclassified as mild (no functional impairment), moderate (functional impairment requiring intervention or therapy), or severe (dependent on assistance).

Statistical Analysis

Treatment group comparisons of mean glucose concentrations at each of the seven perioperative time points were performed on an intention-to-treat basis using linear regression analysis, adjusting for diagnosis (intact ventricular septum *vs.* ventricular septal defect). Proportions of patients with abnormally high ($\geq$ 150 mg/dl [8.25 mM]) or low ($<$ 50 mg/dl [2.8 mM]) glucose concentrations were compared across time points using Fisher exact tests. Perioperative and 1-, 4-, and 8-yr outcomes include both continuous and dichotomous variables. Relations between outcome variables and glucose concentrations were assessed using linear or logistic regression as appropriate, adjusting for diagnosis and treatment group by including them as covariates in the model. Pearson correlation coefficients were used to assess association between serum glucose concentrations and outcomes. The natural logarithms of electroencephalographic reappearance latency times were used to normalize their distributions before analysis. Interaction terms were used to evaluate whether associations between glucose and outcome variables differed for the two treatment groups. Because the analyses were considered exploratory, adjustment was not made for multiple comparisons. For comparisons of patients who did and did not ever have an abnormally high glucose concentration, the power was greater than 90% to detect a difference in means of 0.5 SDs for continuous outcome variables and was greater than 80% to detect a 20% difference in proportions for dichotomous outcomes, using two-sided tests conducted at the 0.05 level of significance.

Results

Perioperative patient characteristics are shown in table 1. Glucose concentrations ranged between 25 and 360 mg/dl. Perioperative glucose concentrations were related to support strategy; therefore, glucose concentrations are presented by support strategy at the measured time points in table 2. Mean values differed significantly between the two support strategy groups after CA or LF at T4 and T5 ($P = 0.01$ and $P = 0.005$, respectively), with a trend toward significance at T6 ($P = 0.07$); higher glucose was associated with longer duration of CA. As presented in table 2, low glucose occurred more frequently at the earlier time points ($P = 0.004$), and higher glucose was more frequent at later times ($P < 0.001$). Five patients had both high and low glucose at various time points. Overall, there were more high values than low values; the 90th percentile for glucose was 160 mg/dl (8.9 mM) or greater at six of the seven time points. Only a few patients (15 of 171 [9%]) required supplementation for glucose less than 50 mg/dl (2.8 mM), and no patient received insulin for hyperglycemia.

Table 1. Descriptive Characteristics of Study Patients

Characteristic	Statistic
Male sex	129 (75%)
Birth weight, g	3,500 (2,250–4,600)
Gestational age, weeks	40 (36–45)
Age at surgery, days	6 (1–67)
Lowest preoperative pH	7.29 (6.90–7.46)
Apgar score at 5 min	9 (5–10)
No. with ventricular septal defect	42 (25%)

Descriptive characteristics of study patients, n = 171, presented as median (range) or number (%).

Glucose Measurements and Electroencephalographic Evaluation

Electroencephalographic monitoring was performed in 138 infants (81%). The correlation between glucose concentration and select electroencephalogram recovery times is shown in table 3. When the entire group was

Table 2. Glucose Concentrations by Support Strategy and Number of Infants with Glucose Concentrations Outside the Range 50 to 150 mg/dl

Time	CA (n = 87)	LF (n = 84)	No. of Infants with glucose $<$ 50 mg/dL	No. of Infants with glucose $\geq$ 150 mg/dL
T1	84 ± 31	86 ± 34	8	10
T2	115 ± 45	123 ± 52	2	35
T3	99 ± 46	110 ± 46	5	21
T4	117 ± 55	98 ± 39*	3	24
T5	141 ± 42	123 ± 36†	0	50
T6	139 ± 43	127 ± 41‡	1	55
T7	145 ± 46	138 ± 43	0	58

Glucose concentrations by treatment group (circulatory arrest [CA] or low-flow bypass [LF]) at seven measurement points presented as mean ± SD in mg/dl. Also shown is the number of infants with abnormal glucose concentrations at each time point. *P* values comparing glucose levels in CA to LF are calculated by linear regression adjusting for diagnosis.

* $P = 0.01$. † $P = 0.005$. ‡ $P = 0.07$.

T1 = after induction of anesthesia and before surgical incision; T2 = 5 min after bypass initiation; T3 = at the onset of circulatory arrest or low-flow bypass; T4 = 5 min after resumption of bypass and the start of rewarming; T5 = at 32°C (rectal) during rewarming; T6 = 10 min after cessation of bypass; T7 = 90 min after end of circulatory arrest or low-flow bypass.

Table 3. Glucose Concentrations and Electroencephalographic Findings

	Time to Close Bursts			Time to Relative Continuous Activity		
Time Points	All Infants	CA	LF	All Infants	CA	LF
T1	−0.28 (0.003)	−0.31 (0.01)	−0.26 (0.11)	−0.16 (0.12)	−0.33 (0.007)	−0.02 (0.98)
T2	−0.14 (0.29)	−0.24 (0.08)	−0.04 (0.91)	−0.04 (0.78)	−0.19 (0.15)	0.09 (0.48)
T3	−0.20 (0.13)	−0.31 (0.02)	−0.04 (0.91)	−0.15 (0.21)	−0.37 (0.003)	0.08 (0.51)
T4	−0.03 (0.34)	−0.29 (0.03)	0.11 (0.21)	−0.11 (0.08)	−0.38 (0.002)	0.10 (0.41)
T5	−0.10 (0.02)	−0.28 (0.02)	−0.10 (0.28)	−0.13 (0.03)	−0.38 (0.002)	−0.03 (0.80)
T6	−0.15 (0.008)	−0.41 (< 0.001)	−0.01 (0.91)	−0.14 (0.06)	−0.43 (< 0.001)	0.10 (0.48)
T7	−0.20 (0.005)	−0.52 (< 0.001)	0.04 (0.80)	−0.13 (0.11)	−0.49 (< 0.001)	0.16 (0.27)

Correlation between serum glucose concentrations and electroencephalographic recovery times for all infants and when separated according to perfusion strategy. Data are reported as Pearson correlation coefficients with *P* values in parentheses; *P* values are adjusted for perfusion status and diagnosis for all infants, and for diagnosis within subgroups. A negative coefficient implies an inverse relation between glucose concentration and time to onset of electroencephalographic activity.

CA = circulatory arrest; LF = low-flow bypass. T1 = after induction of anesthesia and before surgical incision; T2 = 5 min after initiation of bypass; T3 = at the onset of circulatory arrest or low-flow bypass; T4 = 5 min after resumption of bypass and the start of rewarming; T5 = at 32°C (rectal) during rewarming; T6 = 10 min after cessation of bypass; T7 = 90 min after end of circulatory arrest or low-flow bypass.

analyzed collectively, earlier recovery of close bursts was significantly associated with higher glucose concentrations before CA or LF at induction of anesthesia (T1; $P = 0.003$) and from rewarming to 90 min after CA (T5–T7; $P \leq 0.02$). Glucose concentration did not predict time to relative continuous electroencephalographic activity, aside from T5 ($P = 0.03$), or times to first electroencephalogram recovery, continuous pattern, or paroxysmal electroencephalographic activity.

Electroencephalographic outcomes were analyzed by support strategy (table 3). In those infants randomly assigned to CA, earlier recovery of close burst and relative continuous electroencephalographic activity was associated with higher glucose concentrations at all time points ($P \leq 0.03$) other than T2 ($P = 0.08$ and $P = 0.15$, respectively). In the group assigned to LF, no relation was found between glucose and time of onset of close bursts or relative continuous electroencephalographic activity.

Electroencephalographic outcomes were also analyzed with respect to age at surgery (table 4). Although there was no relation in the predominant LF group between age and electroencephalogram recovery time, in the CA group there was a stronger relation between higher glucose and shorter time to close bursts and time to relative continuous activity in neonates aged 7 days or younger compared with infants aged older than 7 days at the time of surgery.

Postoperative electroencephalographic seizure activity was recorded in 27 of 135 infants (20%) who had electroencephalographic evaluations with complete seizure recordings. When comparing glucose concentrations with presence or absence of electroencephalographic seizures, lower glucose concentrations at T6 and T7 (*i.e.*, post CPB) tended to have a higher probability of electroencephalographic seizure activity ($P = 0.06$ and $P = 0.007$, respectively). Figure 1 presents this relation for T7. The area under the receiver–operator characteristic curve corresponding to this model is 0.764 and quantifies how well the model is able to discriminate between patients who did and did not experience electroencephalographic seizures, with 0.5 indicating no predictive power, and 1.0 indicating perfect prediction.

Table 4. Glucose and Electroencephalographic Results by Age at Surgery

	Time to Close Bursts			Time to Relative Continuous Activity		
Time Points	CA Infants	Age at Surgery >7 Days	Age at Surgery ≤7 Days	CA Infants	Age at Surgery >7 Days	Age at Surgery ≤7 Days
T1	−0.31 (0.01)	0.00 (0.94)	−0.41 (0.009)	−0.33 (0.007)	0.00 (0.99)	−0.48 (0.002)
T2	−0.24 (0.08)	−0.08 (0.84)	−0.34 (0.06)	−0.19 (0.15)	−0.11 (0.55)	−0.24 (0.27)
T3	−0.31 (0.02)	−0.20 (0.42)	−0.39 (0.02)	−0.37 (0.003)	−0.37 (0.05)	−0.38 (0.04)
T4	−0.29 (0.03)	−0.21 (0.48)	−0.34 (0.06)	−0.38 (0.002)	−0.43 (0.02)	−0.35 (0.07)
T5	−0.28 (0.02)	−0.30 (0.16)	−0.26 (0.15)	−0.38 (0.002)	−0.38 (0.04)	−0.37 (0.04)
T6	−0.41 (< 0.001)	−0.27 (0.10)	−0.46 (0.004)	−0.43 (< 0.001)	−0.35 (0.08)	−0.48 (0.002)
T7	−0.52 (< 0.001)	−0.23 (0.03)	−0.60 (< 0.001)	−0.49 (< 0.001)	−0.25 (0.21)	−0.59 (< 0.001)

Correlation between serum glucose concentrations and electroencephalographic recovery times for all infants randomized to circulatory arrest (CA) and when separated according to age at surgery in days. Data are reported as Pearson correlation coefficients with *P* values in parentheses; *P* values are adjusted for diagnosis. A negative coefficient implies an inverse relation between glucose concentration and time to onset of electroencephalographic activity.

T1 = after induction of anesthesia and before surgical incision; T2 = 5 min after initiation of bypass; T3 = at the onset of circulatory arrest or low-flow bypass; T4 = 5 min after resumption of bypass and start of rewarming; T5 = at 32°C (rectal) during rewarming; T6 = 10 min after cessation of bypass; T7 = 90 min after end of circulatory arrest or low-flow bypass.

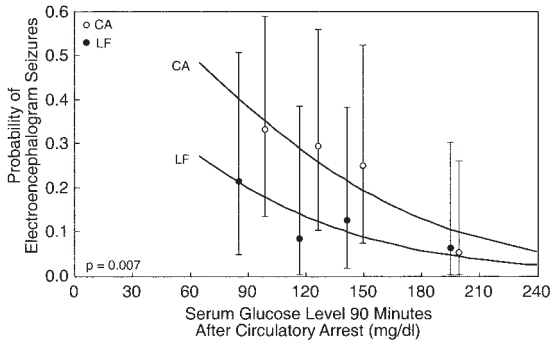

Fig. 1. Estimated probability of electroencephalographic seizure activity as a function of glucose concentration at T7, 90 min after the cessation of circulatory arrest (CA) or low-flow cardiopulmonary bypass (LF). Logistic regression curves are shown by treatment group; the *P* value adjusts for treatment group and diagnosis of ventricular septal defect or intact ventricular septum. The area under the receiver–operator characteristic curve corresponding to this model is 0.764 and quantifies how well the model is able to discriminate between patients who did and did not experience electroencephalographic seizures; an area of 0.5 indicates a model with no predictive power, whereas a model that perfectly predicts outcome every time has an area of 1.0. Point estimates and exact 95% confidence intervals for the probability of seizures are plotted for the mean of each quartile of glucose concentration.

Postoperative Clinical Features

Clinically evident seizures were seen in 11 of 168 of the patients examined (7%); clinical seizures were not related to glucose concentrations measured at any time, although our power to detect a difference was limited by the low overall occurrence of clinical seizures. Postoperative clinical examination revealed possible or definite neurologic abnormalities in 82 of 158 patients (52%). In the patient group as a whole, there was no relation between glucose concentrations and abnormal or possibly abnormal clinical examination. In the CA participants alone, glucose concentrations before the onset of CA, at T1 and T2, were significantly associated with abnormal neurologic examination ($P = 0.03$ and $P = 0.05$, respectively), notably with a lower chance of an abnormal examination associated with higher glucose.

Categorical Glucose Evaluation

The study group was divided into groups for analysis of glucose as a categorical variable: infants with glucose concentrations that were ever high (≥ 150 mg/dl [8.3 mM]; n = 92; 54% of all patients) or were ever low (< 50 mg/dl [2.8 mM]; n = 15; 9% of all patients). Five patients had high and low glucose concentrations at different times; these patients are included in both sets of analyses. Although power is limited in these analyses, electroencephalographic seizure rates did not differ significantly between patients who ever had glucose concentrations of 150 mg/dl (8.3 mM) or greater and those who never had high glucose concentrations (16% *vs.* 25%; $P = 0.20$), or for those who ever had glucose concentrations less than 50 mg/dl (2.8 mM) *versus* those who did not (27% *vs.* 19%; $P = 0.50$). Among 78 infants who had complete neurologic examinations and ever had glucose concentrations of 150 mg/dl or greater, 13 (17%) had definite abnormalities; definite abnormalities were seen equivalently among patients who ever had glucose concentrations of 150 mg/dl (8.3 mM) or greater and those who never had high glucose concentrations (17% *vs.* 23%; $P = 0.57$). There were no clinical seizures in infants with glucose concentrations less than 50 mg/dl (2.8 mM); rates of seizures were equivalent among patients who ever had glucose concentrations of 150 mg/dl (8.3 mM) or greater and those who did not (7% *vs.* 6%; $P = 1.0$).

Late Neurologic and Developmental Outcomes

Of the 171 original participants, 155 returned for 1-yr follow-up, 158 returned at 4 yr, and 156 returned at 8 yr

Table 5. Late Developmental Outcomes

Developmental Testing	All Infants	Glucose Always < 150 mg/dL	Glucose Ever ≥ 150 mg/dL	Normative Data
1 Year				
Psychomotor Developmental Index* (n = 142)	95.1 ± 15.5	95 ± 15	95 ± 16	100 ± 16
Mental Developmental Index* (n = 143)	105.1 ± 15.0	105 ± 13	104 ± 18	100 ± 16
4 Year				
Full-scale IQ (n = 155)†	92.6 ± 14.7	93 ± 15	92 ± 14	100 ± 15
Verbal IQ (n = 155)†	95.1 ± 15.0	95 ± 15	95 ± 15	100 ± 15
Performance IQ (n = 155)†	91.6 ± 14.5	92 ± 15	91 ± 14	100 ± 15
8 Year				
Full-scale IQ (n = 154)†	97.1 ± 15.3	98 ± 15	97 ± 15	100 ± 15
Verbal IQ (n = 154)†	99.8 ± 16.6	100 ± 16	99 ± 17	100 ± 15
Performance IQ (n = 154)†	94.9 ± 14.3	96 ± 14	94 ± 14	100 ± 15

* Second Edition Bayley Scales (1993). †Wechsler (1989).

Summary of developmental data for patients returning 1, 4, and 8 years after surgery for the entire group of infants, for those who at any time point had a high glucose concentration (> 150 mg/dl), and for those who always had a glucose concentration less than 250 mg/dl. The number of patients evaluated is shown in parentheses after the test name. Test scores are provided as mean test value ± SD. Normative data is shown for comparison. There were no significant differences in test scores at any age or related to glucose concentration.

IQ = intelligence quotient.

(table 5). A child with autism was not included in developmental testing. One-year evaluations, including Psychomotor Development Index, Mental Development Index, and Fagan scoring, were not related to perioperative glucose measurements at any time point. Similarly, abnormalities found on 1-yr neurologic examination and MRI were not related to glucose concentrations. Abnormalities on testing performed at 4 yr were not associated with perioperative glucose concentrations. Similarly, at 8 yr, there were no relations between perioperative glucose measurements and neurodevelopmental testing or clinical neurologic examination.

Discussion

In this controlled, prospective, single-institution trial of a homogenous group of infants with D-transposition of the great arteries, we were unable to show a relation between high glucose concentrations and poor early or late neurologic or developmental outcome even after careful adjustment for CA *versus* LF and diagnosis. Notably, some measures of perioperative electroencephalographic activity returned more rapidly in patients with higher glucose concentrations, and lower glucose after CPB correlated with an increased risk of electroencephalographic seizure activity. Our findings were more pronounced in infants who had surgery before 7 days of age. Although postoperative electroencephalographic seizures have been associated with lower Psychomotor Development Index scores and more MRI abnormalities in this patient group,[13] we found perioperative glucose concentrations were not associated with long-term developmental, neurologic, or structural brain abnormalities. Intraoperative glucose could not be correlated with long-term abnormal findings in clinical examination, structural evaluation (MRI), or developmental assessment. Clinical, electroencephalographic, and developmental outcomes were not discernibly different in infants who had either low or high glucose concentrations compared with infants who had normal glucose concentrations throughout.

These findings are in contrast to the adult experience. Adults successfully resuscitated from cardiac arrest with lower glucose concentrations have been reported to have fewer neurologic deficits.[16] After head injury, high glucose concentrations were associated with lower Glasgow coma score and death or persistent vegetative state.[5] One study of adults undergoing open heart surgery found no worse outcome with higher glucose, but the incidence of clinical and neurologic deficits was low, and neurologic testing was limited.[17] Animal studies of induced cardiac arrest have shown lower standardized neurologic scores in animals with high prearrest glucose concentrations,[8] and mature monkeys who received glucose before arrest had more seizures after recovery and more cerebral cortex infarct on pathologic examination.[7]

There are limited data on glucose management in pediatric patients, particularly neonates and infants undergoing cardiac surgery. In 1973, Brown *et al.*[18] described hyperglycemia during deep hypothermic CPB in infants and small children and the effects of administering or withholding dextrose in prebypass intravenous fluids. Steward *et al.*[9] reported that infants with very high preoperative glucose concentrations, *i.e.*, greater than 433 mg/dl (> 24 mM), were more likely to have neurologic impairment after CA; however, the nature of neurologic dysfunction was not specified, patients were heterogeneous in terms of diagnosis and age, and the numbers were too small to allow statistical analysis. Nicolson *et al.*[19] were also unable to show an association between higher preoperative glucose concentrations, or glucose supplementation, and postoperative seizures after CA because their sample was small. In contrast to our study, theirs included fewer infants, electroencephalographic and developmental evaluation were not performed, and follow-up was limited to the in-hospital course.

Another pediatric study reported that higher glucose concentrations before and after CPB and CA correlated with higher postoperative creatine kinase BB[20]; however, glucose concentrations were considerably higher than in our study (mean, 379 ± 27 mg/dl [21 ± 1.5 mM]), and patients were older. Creatine kinase BB is proposed as a nonspecific marker of neuronal injury, but its clinical use remains undefined.[21]

Models of neonatal hypoxic–ischemic brain injury have shown less neurologic injury with higher glucose concentrations, consistent with our results. In cell cultures, glial cells from neonatal rats were more resistant to ischemia if surrounded by glucose concentrations greater than 270 mg/dl (15 mmol/kg).[22] In whole animal experiments, neonatal rats that received glucose just after partial ischemia had 37% less brain infarction by volume.[23] In newborn dogs, hyperglycemia before deep hypothermic CA was not associated with greater cerebral cortex damage compared with normoglycemia.[24] Studies in piglets using MRI spectroscopy suggest glucose utilization in the newborn period is greater than utilization even at several weeks of age.[25,26] The potential beneficial effects of treatment of immature animals with glucose before a hypoxic–ischemic injury (cardiac arrest) are difficult to translate to clinical experience, although some researchers support avoiding hypoglycemia in newborns subject to ischemia because of these animal data.[27] The effect of glucose in immature animals perhaps supports the stronger effect of glucose on early neurologic outcomes in the infants in our study who underwent a primary CA technique as opposed to the LF technique. The stronger relation we found between glucose and time to electroencephalogram recovery in infants aged younger than 7 days in the CA group could suggest that the impact of glucose on ischemic injury

may relate to developmental stage or maturation. Previous pediatric and immature animal data has focused on outcomes after complete arrest; the effect of glucose in low-flow states is less clear.

Hypoglycemia, however, has been shown to be harmful to infants. Low glucose concentrations can cause cerebral infarction in neonates, and MRI and ultrasound imaging show hypoglycemic neonates are three times more likely to have abnormalities than normoglycemic infants.[28] Animal studies support these findings; even mildly low glucose produced more brain injury than normoglycemia in hypoxic-ischemic–injured 7-day-old rats.[10]

The contrast between neonatal and adult data highlights the differences between the mature and immature brain. Glucose is an important metabolic substrate in the immature brain. High glucose increases the accumulation of lactate, and in adults, lactate concentrations greater than 16–20 mmol/kg have been related to brain damage.[29] Immature animal brains do not seem to accumulate lactate in the same way as adults, perhaps because of increased lactate transport capacity across the blood–brain barrier,[30] and lactate clearance may be longer at even 1 month of age than it is in newborns in a piglet model.[31] Furthermore, lactate may be a metabolic substrate for the neonatal brain, thereby also preventing some accumulation.[31] Glucose is released in physiologic stress states; the higher glucose concentrations seen at later measurement points may be related to this effect. The association we found between lower glucose and more electroencephalographic seizures may point to the protective effect of this release in infants. The difference in lactate kinetics, along with the studies of improved outcomes in immature animals with hyperglycemia, supports different perioperative glucose management strategies for infants compared with adults.

There are several limitations of our study. This was an observational study; we did not assign infants to a high- or low-glucose strategy. Therefore, we were only able to determine whether a relation existed between neurodevelopmental outcome and the range of glucose concentrations, rather than with a specific glucose concentration. Second, although we showed a relation between glucose and electroencephalographic outcomes, the correlation coefficients were only good to fair, with none being excellent. This is not surprising because many factors are known to effect electroencephalographic outcomes, including flow rates, hematocrit, and rate of cooling[1–3]; however the demonstration of any relation at all is important as we attempt to optimize perioperative management. In addition, we did not monitor for potential air emboli, which could also contribute to neurologic injury. It is possible that a higher level of hyperglycemia than shown in our study may be required to cause neurologic injury, and we did not try to establish a time-dependent effect related to hyperglycemia. We were unable to find data relating the duration of exposure to hyperglycemia and subsequent neurologic injury or indicating whether spikes in glucose concentration are more significant than prolonged exposure. Few patients had low glucose concentrations, and these were supplemented for concentrations less than 50 mg/dl (2.8 mM). Nevertheless, we believe our results to be relevant because this was a tightly controlled, randomized, and homogeneous patient population with consistent surgical and perioperative care, and there were well-defined early endpoints, long-term monitoring, and little loss to follow-up. Although mean intelligence quotient and other measures of development were close to normal, the range of values was large, indicating that if there were a significant negative effect of high glucose, it should be visible in our sample.

There are important differences between the CPB techniques used in this study more than 10 yr ago and current techniques. This cohort of patients underwent bypass with the α-stat strategy for hypothermic blood gas management and a relatively low hematocrit of 20%. More recent evidence supports the benefit of pH-stat blood gas strategy[32,33] and using a higher hematocrit to reduce neurologic injury during hypothermic CA.[34] Therefore, the incidences of seizures and clinical neurologic abnormalities reported in our study is considerably higher than those of the current institutional experience. However, with a higher incidence of adverse events in this study, we were more likely to detect the effect of glucose concentration on neurologic outcomes.

Our finding that higher glucose was not associated with adverse early or long-term neurologic injury after cardiac surgery and CA has not been previously shown. Similarly, it has not been shown that electroencephalographic seizures after CPB in infants are less likely at higher glucose concentrations, as our data suggest. Our data show that neurologic and electroencephalographic outcomes are not worse in infants with increased glucose. By electroencephalographic criteria, higher glucose may be associated with less early perioperative neurologic injury, and neurodevelopmental outcomes at 1, 4, and 8 yr were not influenced by glucose concentrations. Our data support findings of earlier immature animal studies that hyperglycemia is not detrimental in neonates and infants undergoing CA and does not have to be aggressively treated.

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