Insulin resistance and inflammation are a cause of hyperglycemia after pediatric cardiopulmonary bypass surgery

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ABSTRACT

Objectives: Hyperglycemia is common after pediatric cardiopulmonary bypass (CPB) surgery and is attributed to a state of insulin resistance. We examined the role of CPB-induced inflammation on postoperative plasma glucose, insulin, and the glucose-to-insulin ratio, which was used as a marker of insulin resistance; a decrease in the ratio reflects increased resistance.

Methods: We conducted an ancillary study on a previously published randomized trial of children undergoing CPB surgery. Serial blood glucose, insulin, and cytokines were drawn after CPB and at selected intervals for up to 48 hours after surgery. The primary outcome was plasma insulin levels and glucose-to-insulin ratio. Glucose delivery and feeding status were monitored for potential modifying effects.

Results: The 299 children studied were predominantly male (55%) with a median age of 2.7 (interquartile range [IQR]: 0.5-6.5) years, and weight of 12.6 (IQR: 6.4-10.8) kg. Operations had a median Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery complexity score of 1 (IQR: 1-2) and CPB time of 82 (IQR: 58-122) minutes. Hyperglycemia occurred in 85% of subjects; odds of hyperglycemia peaked at 6 hours after CPB. Plasma glucose was associated with increased insulin and a lower glucose-to-insulin ratio. Increased interleukin (IL)-6 concentrations were associated with increased glucose (estimate [EST]: 0.55 ($\pm$ 0.13) mmol/L; $P < .001$) and insulin (EST: 1.14 ($\pm$ 0.12) μ mol/L; $P < .001$) in linear regression adjusted for repeated measures. Paradoxically, increased cytokines were associated with an increased glucose-to-insulin ratio (EST: 0.21 ($\pm$ 0.03) mmol/ μ mol; $P < .001$).

Conclusions: Hyperglycemia after pediatric CPB surgery is associated with hyperinsulinemia, which may reflect insulin resistance in some patients. Inflammation induced by CPB may play a causative role in insulin resistance. (J Thorac Cardiovasc Surg 2015;150:498-504)

Glucose-to-insulin ratio at various time points during the 48 hours immediately after CPB.

Central Message

Hyperglycemia is common after pediatric cardiopulmonary surgery and may be associated in some patients with insulin resistance (elevated insulin concentrations and a lower glucose-to-insulin ratio).

Perspective

Postoperative hyperglycemia has been associated with increased morbidity and mortality. Efforts to address this relationship have been unsuccessful. This article describes the pathophysiologic driver of this relationship, for some children. We hope these findings help identify patients likely to benefit from targeted intervention.

See Editorial Commentary page 505.

Supplemental material is available online.

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Critical illness hyperglycemia (CIH) is common after pediatric cardiopulmonary bypass (CPB) surgery, and is associated with increased morbidity and mortality.^{1,2} Despite some evidence supporting improved clinical outcomes with tight glycemic control in both pediatric and adult populations,^{3,4} the data overwhelmingly counter aggressive glucose management as a universal strategy.⁵⁻⁷ This discrepancy might reflect the multifactorial underpinnings of CIH, such that not all patients benefit from a single therapeutic intervention, although some might. Determining the validity of this

Abbreviations and Acronyms

CI	= confidence interval
CIH	= critical illness hyperglycemia
CPB	= cardiopulmonary bypass
EST	= estimate
ICU	= intensive care unit
IL	= interleukin
IQR	= interquartile range
OR	= odds ratio
STS-EACTS	= Society of Thoracic Surgery– European Association for Cardio- Thoracic Surgery

assertion requires studies of the mechanisms of hyperglycemia, rather than just simple associations or even response to a uniformly applied treatment.

Insulin resistance has been implicated as a central cause of CIH in several critically ill populations, including those with severe burns,⁸⁻¹⁰ and even neonates after CPB.¹¹ Hormonal dysregulation, marked by elevated plasma glucagon, cortisol and catecholamine concentrations, has been associated with a decrease in peripheral insulin sensitivity and systemic hyperglycemia.¹² Patients undergoing CPB have demonstrated similar alterations in circulating glucagon, cortisol, and catecholamine levels,¹¹ and although an increase in circulating insulin has been found, the question of whether insulin resistance provides a link between glucose metabolism and adverse outcomes in this population has not been extensively investigated.

Systemic inflammation has recently been associated with hyperglycemia and insulin resistance in the adult diabetic population. CPB is known to initiate profound systemic inflammation that may have similar associations with glucose metabolism; a linkage has been suggested among inflammation, insulin resistance, and outcomes after congenital heart surgery.¹¹ We therefore sought to describe the relationships among hyperglycemia, plasma insulin concentrations, insulin resistance, and inflammation, in a prospective cohort of children undergoing CPB surgery for congenital heart disease. We hypothesized that CPB-induced inflammation was associated with hyperinsulinemia and insulin resistance, which would, in turn, be associated with postoperative hyperglycemia.

METHODS**Patient Selection and Setting**

This ancillary observational study was conducted on a cohort previously enrolled in a randomized study examining the effects of preoperative remote ischemic preconditioning on children undergoing CPB surgery.¹³ The results of that study showed no clinical, inflammatory, or hormonal differences between those who received preconditioning and those who did not. Consequently, the present study was performed without regard to whether the subject received preconditioning. The study was approved by our institution's

research ethics board and was conducted with subjects who were admitted to our cardiac intensive care unit after undergoing CPB surgery. Informed consent was obtained from parent, guardian, or patient prior to surgery in accordance with our institution's policies.

Patients were eligible if they were aged <18 years. Children were excluded if they had preoperative arterial obstruction leading to compromised blood flow to a limb, major organ, or major artery, or if they suffered cardiovascular collapse requiring intervention. Patients were excluded if they had organ dysfunction requiring medical intervention, clotting disorder, pulmonary disease, infection within 1 week of repair, a genetic abnormality or syndrome, or if they had received systemic glucocorticoid therapy within 10 days of surgery.

Perioperative steroids were administered according to the usual institutional practice; neonatal subjects (aged <28 days) received intravenous 10 mg/kg methyl-prednisolone at 12 and 2 hours before repair, and all subjects undergoing deep hypothermic circulatory arrest received a methyl-prednisolone dose (30 mg/kg) in the CPB prime. Standard blood-based cardioplegia, incorporating 30 U/L of insulin, was used. Regional cerebral perfusion was provided during periods of circulatory arrest, according to usual practice. Postoperative care proceeded according to routine clinical practice. Postoperative use of corticosteroids for hemodynamic instability, and insulin administration for glycemic control, were left to the discretion of the critical care team.

Monitoring

Serial blood samples were collected at predetermined time intervals (at critical care admission; and at 3, 6, 12, 24, and 48 hours). Plasma glucose, insulin, glucagon, cortisol, and cytokine concentration (including IL-1- α , IL-6, IL-8, IL-10, and tumor necrosis factor- α) were measured at each time point. Quantitative cytokine measurements were performed using MILLIPLEX MAP human cytokine kits (Millipore, Billerica, Mass) on a Luminex 200 system using xPONENT 3.1 software (both from Luminex Corp, Austin, Tex), per manufacturer instructions. Quantification was performed by the Analytical Facility for Bioactive Molecules of the Centre for the Study of Complex Childhood Diseases, The Hospital for Sick Children, Toronto, Canada.

Subjects were monitored for glucose delivery and feeding status. Parenteral glucose delivery, generally in 5% dextrose infusions, was measured in mg/kg/minute and included all infusions, medications, and parenteral nutrition. Hyperglycemia was defined as a plasma glucose concentration above the upper limit of normal for age. This condition was further characterized by severity, with mild hyperglycemia defined as above the upper limit of normal for age, but <180 mg/dL; moderate as 180-270 mg/dL; and severe as >270 mg/dL.

Outcomes

Postoperative plasma insulin concentration and the glucose-to-insulin ratio were used as the primary outcome. This simple measure of insulin resistance has been used in research with several populations, including those who have metabolic syndrome and those who have polycystic ovarian disease.^{14,15} A lower value reflects increased resistance, as higher insulin concentrations are necessary to achieve similar glucose levels. In addition to glucose and insulin concentrations, operative and perioperative clinical variables were recorded. Intervals of care, including length of intensive care unit and hospital stay, were measured as secondary outcome variables.

Statistical Analysis

All demographic data were described as mean with SD, median with interquartile range, or frequency, as appropriate. All measures of glycemia or cytokines were transformed using natural logarithms. Given the repeated and variable blood sampling per patient, all regression models that were used to determine the direction and strength of associations between potential predictor variables (including demographic and operative factors previously shown to affect hyperglycemia, cytokine concentrations, hormone concentrations—insulin, glucagon, cortisol—and glucose-to-insulin ratio)

and hyperglycemia included a compound symmetry covariance structure. To determine the association between time-dependent postoperative outcomes and early postoperative glycemic parameters or inflammatory cytokines, repeated measures taken during the first 48 hours were averaged. All statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary NC).

RESULTS

A total of 299 subjects were enrolled from April 2008 through May 2011. The demographic and surgical characteristics are presented in Table 1. Subjects were mostly male (55%), with a mean age of 2.7 (IQR: 0.5-6.5) years. Subjects underwent operations of relatively low complexity, with a CPB time of 82 (range: 58-122) minutes. The most common operations were for repair of ventricular septal defects and Tetralogy of Fallot (Table 1). Subjects were ventilated for a median (IQR) duration of 19 (IQR: 14-30) hours and were discharged from the intensive care after 33 (IQR: 33-57) hours after admission (Table E1). Nearly two thirds of subjects were censored by the end of study, with only 102 subjects providing a complete set of samples for up to 48 hours of observation.

Exogenous insulin was administered to only 6 subjects, accounting for 6 of 1378 observations throughout the entire study period. Postoperative steroids were given to 13 subjects during the study, accounting for 30 observations. Hydrocortisone was used in 6 subjects (18 observations) for inotrope/pressor refractory shock; 7 subjects received dexamethasone (12 observations) for relief of upper airway edema. Those subjects who received postoperative steroids were started at a median of 24 (IQR: 12-48) hours after CPB.

Plasma Glucose, Insulin, and Glucose-to-Insulin Ratio

Mean plasma glucose concentrations rose after CPB, to a peak of 158 ± 52 mg/dL at 6 hours, and then decreased to 104 ± 31 mg/dL by 48 hours. Plasma glucose was not associated with the rate of glucose infusion. After accounting for common change over time, no statistically significant association was found between plasma glucose and inotropic score in linear regression models adjusted for repeated measures. Plasma glucose was not associated with use of perioperative steroids. Approximately 85% of subjects had ≥ 1 elevated glucose measurement within the 48-hour observation period; 35% and 6% of subjects had ≥ 1 episode of hyperglycemia in the moderate and severe hyperglycemia range, respectively. The incidence of moderate and severe hyperglycemia varied over time (Figure 1). The odds of moderate or severe hyperglycemia were highest at 6 hours (OR 1.52; 95% CI: 1.02-2.26), and lowest at 48 hours (OR 0.08; 95% CI: 0.02-0.32).

Plasma insulin concentration rose rapidly in the first 12 hours after surgery (6.03 ± 0.82 μ mol/L/hour,

TABLE 1. Patient demographics and surgical characteristics

Patient and surgery characteristic	Value
Patients	
Gender, male	164 (55)
Height (cm)	88 (65-116.5)
Weight (kg)	12.6 (6.4-20.8)
Age at surgery (y)	2.7 (0.5-6.5)
Surgery	
Repair of ventricular septal defect	50 (17)
Repair of Tetralogy of Fallot	33 (11)
Fontan operation	31 (10)
Repair of AVSD (secundum/sinus venosus)	24 (8)
Arterial switch operation	17 (6)
Repair of primum AVSD	15 (5)
Mitral valve repair or replacement	15 (5)
Pulmonary valve replacement	14 (5)
Repair of complete AVSD	13 (4)
Repair of partial anomalous pulmonary venous repair	12 (4)
Aortic valve repair	11 (4)
Right ventricular to pulmonary artery conduit	10 (3)
Aortic valve replacement	7 (2)
Right ventricular outflow tract repair	7 (2)
Repair of total anomalous pulmonary venous repair	7 (2)
Subaortic myectomy	6 (2)
Repair of double outlet right ventricle	6 (2)
Pulmonary arterial plasty	5 (2)
Repair of aortic arch	5 (2)
Repair of truncus arteriosus	3 (1)
Repair of interrupted aortic arch	2 (1)
Bidirectional cavo-pulmonary shunt	1 (0.33)
Repair of ALCAPA	1 (0.33)
Tricuspid valvuloplasty	1 (0.33)
Repair of coronary artery stenosis	1 (0.33)
Rastelli operation	1 (0.33)
SVC reconstruction	1 (0.33)
Surgical complexity	
STS-EACTS score	
1	173 (58)
2	54 (18)
3	47 (16)
4	24 (8)
Cardiopulmonary bypass time (min)	82 (58-122)
Crossclamp time (min)	63 (32-94)
Deep hypothermic circulatory arrest	12 (4)

Categorical data are reported as n (%); continuous data are reported as median (interquartile range), or as mean ($\pm$ SD), according to distribution. AVSD, Atrioventricular septal defect; ALCAPA, anomalous left coronary artery from the pulmonary artery; SVC, superior vena cava; STS-EACTS, Society of Thoracic Surgery–European Association for Cardio-Thoracic Surgery.

$P < .001$), and it plateaued thereafter. Plasma insulin concentration was associated with exogenous insulin infusion (EST: 1.4 U/kg/hour; 95% CI: 0.4-2.4; $P = .01$) based on univariable regression models adjusted for repeated measures and adjusted for time from CPB. Plasma insulin was not associated with glucose infusion rate (EST: 7.7 mg/kg/minute; 95% CI: -1.4 to 17 ; $P = .1$); perioperative steroid delivery (EST: 65; 95% CI: -10 to 141 ; $P = .09$), or

FIGURE 1. The incidence of postoperative hyperglycemia at various time points during the 48 hours immediately after CPB: moderate hyperglycemia (>180 mmol/L; black); severe hyperglycemia (>270 mmol/L; gray). CPB, Cardiopulmonary bypass.

postoperative inotrope score (EST: 2.4; 95% CI: -0.2 to 5; $P = .07$).

Mean ($\pm$ SD) glucose-to-insulin ratio decreased after CPB, from 0.54 ± 0.13 at 3 hours to 0.44 ± 0.09 at 48 hours (Figure 2). Glucose-to-insulin ratio was not associated with exogenous insulin infusion but was weakly associated with exogenous glucose delivery (EST: 0.02 mg/kg/minute; 95% CI: 0.009-0.02; $P = .001$).

Glucose Delivery and Feeds

All subjects were given glucose through dextrose-based infusions, with the majority (90%) started within the first 3 hours of admission, at a median (IQR) rate of 1.49 (0.97-1.89) mg/kg/minute. Median glucose infusion rate peaked at 1.52 (IQR: 1.09-1.92) mg/kg/minute at 6 hours after admission, decreasing to 0.57 (IQR: 0.07-1.41)

FIGURE 2. Glucose-to-insulin ratio at various time points during the 48 hours immediately after CPB is shown, from linear regression models adjusted for repeated measures over time, and variable sampling through a compound symmetry covariance structure. Circles represent estimated average values; bars represent SDs. CPB, Cardiopulmonary bypass.

FIGURE 3. Cytokine concentrations at various time points during the first 48 hours immediately after CPB. Plasma IL-6 (blue) and plasma TNF- α (red) concentrations are from linear regression models adjusted for repeated measures over time, and variable sampling through a compound symmetry covariance structure. Squares and circles represent estimated average values; bars represent SDs. Offset of times 0 (immediately after end of CPB) and 48 hours are for visual purposes only; data were collected at the same time points. IL, Interleukin; TNF, tumor necrosis factor; CPB, cardiopulmonary bypass.

mg/kg/minute at 48 hours. Feeds were initiated for 281 subjects at a median time of 24 (IQR: 12-24) hours after CPB. The proportion of subjects receiving enteral feeding increased progressively during the study period from <0.5% (1 of 298) at 3 hours after admission to 82% (97 of 119) at 48 hours. Overall, the odds of feeding increased significantly over time (OR: 1.133; 95% CI: 1.109-1.157; $P < .001$).

Relationships Among Glucose, Insulin, and Glucose-to-Insulin Ratio

Higher plasma glucose was associated with an increase in plasma insulin concentration (EST: 0.18 ($\pm$ 0.01) ln μ mol/L of insulin per ln mg/dL glucose, $r^2 = 0.18$, $P < .001$) (Figure E1). This relationship was not associated with the rate of glucose infusion, feeding status, or hyperglycemia, but was affected by surgical complexity. In multivariable models accounting for time from CPB, STS-EACTS (Society of Thoracic Surgery-European Association for Cardio-Thoracic Surgery complexity) score did not affect the association between glucose and plasma insulin.

Associations Among Postoperative Inflammation, Glucose, Plasma Insulin, and Glucose-to-Insulin Ratio

Cardiopulmonary bypass was associated with a systemic inflammatory response with an increase in all measured cytokines. Cytokine concentrations rose immediately after surgery, peaking by 3 hours and gradually decreasing during the 48-hour observation period (plasma IL-6 and tumor necrosis factor- α shown in Figure 3). Linear regression

TABLE 2. Association between postoperative change in inflammatory cytokines and change in plasma glucose, plasma insulin, and glucose-to-insulin ratio

Cytokine	Glucose			Insulin			Glucose-to-insulin ratio		
	EST	SE	P value	EST	SE	P value	EST	SE	P value
IL-6	0.550	0.131	<.001	1.135	0.119	<.001	0.210	0.029	<.001
IL-8	0.454	0.100	<.001	1.441	0.172	<.001	0.366	0.39	<.001
IL-10	0.947	0.161	<.001	0.534	0.125	<.001	0.297	0.023	<.001
IL-1- α	0.097	0.103	.35	0.054	0.232	.82	0.012	0.031	.70
TNF- α	0.142	0.071	.04	−2.330	0.332	<.001	0.544	0.050	<.001

Parameter EST and associated SE represent the change in cytokine concentration (in log pg/mL) for increasing plasma glucose, plasma insulin, and glucose-to-insulin ratio obtained from linear regression models adjusted for repeated measures and variable sampling through a compound symmetry covariance structure. EST, Estimate; SE, standard error; IL, interleukin; TNF, tumor necrosis factor.

models, adjusted for repeated measures through a compound symmetry covariance structure, demonstrated that change over time in plasma IL-6 (EST: 0.55 (0.13) log pg/mL per 1 log mg/dL; $P < .001$); IL-8 (EST: 0.45 (0.10) log pg/mL per 1 mg/dL; $P < .001$); and IL-10 (EST: 0.95 (0.26) log pg/mL per 1 mg/dL; $P < .001$) concentrations were correlated with change over time in plasma glucose (Table 2). Peak cytokine levels, including IL-8, IL-10, and tumor necrosis factor- α , were associated with increased surgical complexity (Table E2). Higher cytokine concentrations, including IL-6, IL-8, and IL-10, were additionally associated with higher plasma insulin concentration only when subjects received low glucose infusion rates (<0.26 mg/kg/minute) or nil per os. Higher cytokine levels were associated with higher glucose-to-insulin ratios, representing reduced insulin resistance. No association was observed between plasma tumor necrosis factor- α and plasma glucose, insulin, or glucose-to-insulin ratio.

Associations With Outcomes

No consistent relationships were detected among plasma glucose, plasma insulin, or glucose-to-insulin ratio, and intervals of care. In multivariate models accounting for numerous predictors, including age, weight, STS-EACTS complexity score, duration of CPB, crossclamp time, and deep hypothermic circulatory arrest, an increase average glucose-to-insulin ratio during the first 48 hours after surgery was associated with a shorter ventilation duration (EST: -0.78 ; 95% CI: -1.11 to -0.45 log hours; $P < .001$) and shorter hospital admission (EST: -0.38 ; 95% CI: -0.66 to 0.09 log hours; $P = .01$). In these models, a higher average, during the first 48 hours after surgery, in plasma insulin level was associated with only longer duration of ICU admission (EST: 0.11 ; 95% CI: 0.07 - 0.14 log hours, $P < .001$). Only higher average IL-8 was associated with increased morbidity, including higher 48-hour average inotropic score, longer ventilation, ICU length of stay, and hospitalization.

DISCUSSION

Critical illness hyperglycemia often has been attributed to a state of insulin resistance and altered glucose

handling.¹⁶ This study of 299 children after cardiac surgery supports the notion that hyperglycemia in children undergoing CPB may be a manifestation of increased insulin resistance, as observed by a postoperative increase of plasma insulin in the presence of a lower glucose-to-insulin ratio. The findings further suggest that these alterations to glucose metabolism are associated with the height of the systemic inflammatory response incited by CPB.

Insulin resistance in postoperative CPB pediatric patients has been suspected since Anand and colleagues¹⁷ demonstrated an increased plasma insulin concentration in neonates after cardiac surgery. In that study, insulin concentration peaked at 6 hours after the operation and did not return to baseline by the end of the 24-hour observation period. Surviving subjects showed a trend toward lower peak insulin, compared with nonsurvivors. Nevertheless, insulin resistance cannot be diagnosed by hyperinsulinemia alone; it must account for the relationship between insulin concentration and corresponding glucose levels.

The gold standard physiologic measurement of insulin resistance is the euglycemic insulin clamp, during which subjects receive a constant insulin infusion while glucose delivery is titrated, until a state of stable, normal glucose levels is achieved. Insulin sensitivity is quantified according to the magnitude of glucose infusion needed to maintain normoglycemia. The euglycemic insulin clamp technique has been used in the perioperative CPB setting, primarily to achieve tight glycemic control, rather than to evaluate insulin resistance.^{18,19}

These studies reveal the difficulty of maintaining stable glucose concentrations during the perioperative period, likely owing to the rapid fluctuations in underlying glucose metabolism associated with CPB. The Homeostasis Model Assessment and its subsequent iterations are another widely used biochemical measure of insulin resistance.²⁰ A computer-based algorithm is used to derive beta-cell function and insulin resistance from plasma glucose and insulin concentrations sampled under fasting, steady-state conditions. Use of this assessment model would therefore be inappropriate in the rapidly evolving postoperative patient.

The glucose-to-insulin ratio was considered the most appropriate measure of insulin resistance for our study. This ratio is easily measured and can be used in children immediately after cardiac surgery, a setting of evolving physiology during which the use of a euglycemic insulin clamp may not be safe or feasible. The inverse ratio—of insulin to glucose—has in fact been used in several studies exploring CIH in children.²¹⁻²³ The insulin-to-glucose ratio was used to examine the CIH occurring during respiratory failure²¹ and after pediatric CPB surgery^{22,23}; the glucose-to-insulin ratio was therefore chosen as the marker of insulin resistance for this study.

Verhoeven and colleagues²² quantified insulin concentration and the insulin-to-glucose ratio, before surgery and through the first 24 hours of recovery, in a study of 49 children undergoing cardiac surgery for noncyanotic congenital heart disease.²² Of the 52% of subjects who experienced postoperative hyperglycemia, only 9% were found to have an insulin-to-glucose ratio >18 , marking the limit of insulin resistance; however, blood sugar in all subjects had normalized by the end of the study period. Plasma insulin concentration rose sharply after CPB and remained elevated throughout the study. The average insulin-to-glucose ratio increased after separation from CPB.

Our study has several findings similar to those of Verhoeven and colleagues.²² The incidence of postoperative hyperglycemia was high, with 85% of subjects having ≥ 1 elevated measurement during the period of observation. The time course of hyperglycemia was similar, with peak odds of hyperglycemia and highest mean glucose concentration occurring at 6 hours after surgery. The plasma insulin concentration rose rapidly after surgery, but unlike some previous studies, the insulin level did not decrease significantly within the first 48 hours.

Plasma insulin remained elevated, and the glucose-to-insulin ratio showed a progressive decline throughout the observation period. Verhoeven and colleagues²² attributed this late increase in plasma insulin and the insulin-to-glucose ratio to improving health and the initiation of enteral feeds.²² In support of this notion, we found that the odds of receiving enteral feeds increased, in parallel to the rise in plasma insulin. Feeding status, however, did not modify the relationship between glucose and plasma insulin, or between plasma insulin and glucose-to-insulin ratio, in this cohort.

Alternatively, these findings may reflect a selection bias in the population sampled. Healthier patients were extubated earlier, discharged rapidly from the intensive care unit, and censored from the study whereas younger, sicker subjects remained in the study longer. If CIH was caused by insulin resistance only in sicker patients, the expected relationships among glucose, insulin, and glucose-to-insulin ratio would become evident over time, with censoring of nonaffected subjects.

This theory is supported by the finding that an increase in glucose was associated with an even greater rise in plasma

insulin, as the time from CPB increased. Equally, a higher plasma insulin level was associated with a larger drop in the glucose-to-insulin ratio further out from surgery. This finding additionally suggests that only a minority of patients, particularly those who are sicker and manifest evidence of insulin resistance, benefit from intensive insulin therapy. This possibility might explain the absence of a demonstrable benefit for universal implementation of tight glycemic control in this population.^{5,6} Early identification of patients at risk for insulin resistance, and targeted tight glycemic control, may thus be a way to improve clinical outcomes.

The initiation of CPB incites a systemic inflammatory response mediated in large part through release of cytokines, including IL-6, IL-8, and tumor necrosis factor- α .²⁴ Although high concentrations of these pro-inflammatory cytokines have been associated with hyperglycemia and insulin resistance under numerous physiologic conditions, this study proposes a more-complex relationship among inflammation, glucose, and insulin resistance. Subjects in this study exhibited the expected inflammatory response with cytokine concentrations rising immediately after surgery, peaking at 3 hours after CPB and decreasing thereafter. This trajectory paralleled the incidence of hyperglycemia and the increase in plasma insulin. Linear regression models adjusted for repeated measures showed a positive association between cytokines and plasma glucose, and between insulin and the glucose-to-insulin ratio. This suggests that inflammation is associated with increased insulin, but hyperglycemia in this setting may also occur by a process other than insulin resistance, making the role of inflammation in the causative pathway unclear.

The height of the inflammatory response was found to increase in proportion to surgical complexity, suggesting that the relationship between inflammation and insulin regulation is particularly important in sicker patients. This observation is in direct contrast to 2 separate randomized studies^{3,11} of tight glycemic control in children, in which intensive insulin therapy was associated with attenuation of systemic inflammation, marked by lower levels of C-reactive protein, IL-6, and IL-8. A similar response was observed in a randomized study of intraoperative infusion of high-dose insulin in adults undergoing CPB surgery.²⁵

These studies suggest that the inflammatory response is a consequence of insulin resistance and hyperglycemia, or that it is an element in a positive feedback loop. However, unlike our study, both of these studies^{3,11} of intensive insulin therapy included mainly infants (aged <1 year) and may represent a different or sicker population. Although one half of the subjects in this study were randomized to receive preoperative remote ischemic preconditioning, postoperative glucose, cytokine, and hormone levels did not differ across these arms and therefore would not have played a role in our findings.¹³

Hyperglycemia, hyperinsulinemia, glucose-to-insulin ratio, and inflammation did not seem to affect clinical outcome measures in this study. This finding is in contrast to those of a previous study in which the peak concentration and duration of hyperglycemia were shown to be strongly associated with increased morbidity.² This difference may be attributed to lower surgical complexity in the current study. A high preoperative insulin concentration, and a low glucose-to-insulin ratio, have been associated with increased postoperative morbidity²³; however, baseline values were not taken in our study, and therefore, the preoperative metabolic state could not be assessed. A lower glucose-to-insulin ratio was associated with the duration of mechanical ventilation and hospital admission, but it was not associated with other intervals of care. The general low incidence of morbidity in this cohort precluded accurate assessment of the clinical impact of hyperinsulinemia and the glucose-to-insulin ratio.

This study has several limitations that merit further exploration. Enrolled subjects received routine postoperative care; healthier subjects had invasive lines removed sooner and therefore were not included in the period of observation. The observed hyperinsulinemia and possible insulin resistance may therefore reflect a selection bias and be limited to only those who are less well. Subjects enrolled in this study did not undergo preoperative blood sampling. As a result, baseline glucose, insulin, and insulin sensitivity were not measured and could not be accounted for in the analyses. Finally, because the study was conducted at a single center, subjects may have been influenced by institution-specific practices that could have altered the relationships among plasma glucose, insulin, and the glucose-to-insulin ratio.

CONCLUSIONS

Cardiopulmonary bypass is associated with hyperglycemia and hyperinsulinemia. Insulin resistance, reflected by a lower glucose-to-insulin ratio, may be associated with postoperative CIH in some subjects, but it may not be the sole explanation for postoperative hyperglycemia. The role of the postoperative inflammatory response is unclear, as an association was found of plasma glucose to insulin, but paradoxically to less insulin resistance. Further study is required to examine the relationships among inflammation, glucose, and insulin resistance in a higher-risk population and to delineate the association of these factors with morbidity and clinical outcomes.

Conflict of Interest Statement

Steven M. Schwartz reports consulting fees from Novartis AG. All other authors have nothing to disclose with regard to commercial support.

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Key Words: cardiopulmonary bypass, hyperglycemia, hyperinsulinemia, insulin resistance, pediatrics

FIGURE E1. Scatterplot comparing log-transformed plasma glucose to log-transformed plasma insulin concentrations ($r^2 = 0.18$; $P < .001$).

TABLE E2. Association between average postoperative cytokine concentrations and surgical complexity

Cytokine	STS-EACTS complexity score			CPB time		
	EST	SE	P value	EST	SE	P value
IL-6	−0.790	0.075	.29	−0.0017	0.0014	.22
IL-8	0.167	0.041	<.001	0.0025	0.0009	.003
IL-10	0.130	0.043	.003	0.0039	0.0008	<.001
IL-1- α	−0.005	0.082	.97	−0.0010	0.0015	.49
TNF- α	0.092	0.032	.004	0.0023	0.0006	<.001

Parameter ESTs and associated SE represent the change in average postoperative cytokine concentration (in log pg/mL) estimates from linear regression models adjusted for repeated measures and variable sampling through a compound symmetry covariance structure. STS-EACTS, Society of Thoracic Surgery–European Association for Cardio-Thoracic Surgery; CPB, cardiopulmonary bypass; EST, estimate; IL, interleukin; TNF, tumor necrosis factor; SE, standard error.

TABLE E1. Patient outcomes

Postoperative management	Value
Inotrope score	3.3 (0-6.6)
Exogenous insulin infusion	6 (2)
Steroid administration	17 (6)
Outcome	
Systemic infection	11 (4)
Renal failure	0 (0)
Seizure	3 (1)
Cardiac arrest	1 (1)
ECMO	1 (1)
Death	0 (0)
Ventilation time (h)	19 (14-30)
ICU length of stay (h)	33 (33-57)
Hospital length of stay (d)	5 (3-8)

Values are n (%), or median (interquartile range). ECMO, Extracorporeal membrane oxygenation; ICU, intensive care unit.