Glycemic profile in infants who have undergone the arterial switch operation: Hyperglycemia is not associated with adverse events

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Objective: Tight glycemic control improves outcomes in critically ill adults. There are limited data regarding the effect of glycemic profiles in infants after cardiac operations. The aim of this study was to evaluate the association of hyperglycemia and hypoglycemia on adverse events in infants undergoing the arterial switch operation.

Methods: From 2000 through 2005, 93 infants underwent the arterial switch operation (mean age, 2.5 ± 5.9 weeks; mean weight, 3.4 ± 0.8 kg). All serum glucose values during the first 24 postoperative hours were documented. The effect of time spent in specific glycemic bands on adverse events was determined.

Results: Twenty-three (25%; group 1) infants spent more than 50% of the time with glucose values between 80 and 110 mg/dL, and 13 (14%; group 2) spent more than 50% of the time with glucose values of greater than 200 mg/dL. A total of 71 adverse events was documented in 45 (48%) of 93 infants. Group 1 infants were more likely to have any adverse event ($P = .001$) and renal insufficiency ($P < .001$). Group 2 infants were not more likely to have adverse events. When controlling for preoperative and operative factors, being in group 1 was an independent predictor of postoperative adverse events ($P = .004$).

Conclusion: Hyperglycemia does not appear to be detrimental in postoperative infants with congenital heart disease. Infants who spent the majority of the time with glucose values between 80 and 110 mg/dL were at increased risk for adverse events. The ideal glycemic profile in the postoperative cardiac infant has yet to be defined.

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Serum hyperglycemia has been associated with increased morbidity and mortality in many pathophysiologic states in critically ill adults and children, including sepsis,¹ myocardial infarction,^{2,3} and stroke.⁴ Adults undergoing cardiac operations also have increased morbidity with intraoperative hyperglycemia.^{5,6} Additionally, tight glycemic control with intensive insulin therapy in certain populations of adult patients, including patients after cardiac operations, significantly improves morbidity and mortality.⁷ Importantly, hyperglycemia has not been demonstrated to be a risk factor in other critically ill populations, including patients in general medical and surgical intensive care units.^{8,9} Additionally, it is unclear whether short-term hyperglycemia in children is significantly detrimental.¹⁰ Infants are more reliant on glucose for energy use and have a decreased ability to use alternative energy substrates,

Abbreviations and Acronyms

AE	= adverse event
APC	= activated protein C
ASO	= arterial switch operation
CVICU	= cardiovascular intensive care unit
LOS	= length of stay
SGV	= serum glucose value

such as fatty acids.¹¹ Moreover, aggressive treatment of hyperglycemia results in more episodes of hypoglycemia,¹² which can be particularly detrimental to the neonatal myocardium and central nervous system.¹³⁻¹⁵

There are very limited data regarding the glycemic profile of infants after cardiac operations. Furthermore, whether hyperglycemia or hypoglycemia is associated with increased adverse events (AEs) has not clearly been elucidated. Therefore the purpose of our study was to define the glycemic profile of infants undergoing the arterial switch operation (ASO) and to evaluate the association of hyperglycemia and hypoglycemia with AEs.

Materials and Methods

From January 1, 2000, through October 31, 2005, 93 infants underwent the ASO at Texas Children's Hospital, and their medical records were reviewed. The mean gestational age at birth was 38.7 ± 1.8 weeks, and the mean age at the time of the operation was 2.5 ± 5.9 weeks. There was 1 (1%) operative mortality. Five patients underwent delayed sternal closure. Baseline cohort characteristics are shown in Table 1. The cardiac anatomic diagnoses were dextro-transposition of the great arteries with ventricular septal defect (n = 55; 59%) and intact ventricular septum (n = 31; 33%). There were 7 (8%) patients with double-outlet right ventricles with subpulmonic ventricular septal defects (Taussig-Bing anomaly). Most patients underwent a balloon atrial septostomy (82%) and were weaned from prostaglandin infusions (51%) before their operations. The operative profile is shown in Table 2.

Baseline demographic and medical data were collected, including gestational age, weight, cardiac diagnosis, coronary artery anatomy as classified by Yacoub and Radley-Smith,¹⁶ and preoperative condition. Operative data collected included the cardiopulmonary bypass time, the aortic crossclamp time, the use of phenoxybenzamine, and the use of corticosteroids. The techniques of anesthesia, cardiopulmonary bypass, and surgical intervention were standardized in all patients and have been described previously.¹⁷ Steroids during cardiopulmonary bypass were administered at the discretion of the attending surgeon. Postoperative maintenance fluids consisted of half-normal saline with 10% dextrose infusing at $1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. A comprehensive review of postoperative morbidities was performed. It was unit policy not to administer insulin to treat hyperglycemia.

All serum glucose values (SGVs) for the first 24 hours postoperatively were collected. SGVs were obtained every 4 hours postoperatively, with additional values obtained at the discretion of the attending cardiac intensivist. The glycemic profile was divided into 6 bands: less than 80 mg/dL, 80 to 110 mg/dL, 111 to 150

TABLE 1. Preoperative characteristics (n = 93)

Demographic data	
Female sex, n (%)	33 (35)
Gestational age, wk	38.7 ± 1.8
Age at operation, wk	2.5 ± 5.9
Birth weight, kg	2.9 ± 1.2
Weight at operation, kg	3.4 ± 0.8
Anatomic descriptors	
D-TGA with IVS, n (%)	31 (33)
D-TGA with VSD, n (%)	55 (59)
Taussig-Bing anomaly, n (%)	7 (8)
Yacoub type A coronary arteries, n (%)	60 (65)
Yacoub type D coronary arteries, n (%)	22 (24)
Single coronary artery, n (%)	8 (9)
Intubated preoperatively, n (%)	26 (28)
Preoperative interventions	
Balloon atrial septostomy, n (%)	76 (82)
Inotropes, n (%)	33 (35)
Prostaglandin discontinued before operation, n (%)	48 (51)

D-TGA, Dextro-transposition of the great arteries; IVS, intact ventricular septum; VSD, ventricular septal defect.

mg/dL, 151 to 199 mg/dL, 200 to 250 mg/dL, and greater than 250 mg/dL. Given that patients had a variety of SGVs recorded in several bands over this time period, the percentage of time spent in each glycemic band was calculated similarly to the technique described by Finney and colleagues.¹⁸ Because there might be multiple SGV measurements made when values deviate significantly from normal, recording the absolute number of SGVs in a given glycemic band might overestimate the time spent with very high or very low SGVs. Thus time weighting was used with linear interpolation by assuming a linear trend between 2 SGVs. This permitted the percentage of time spent in each glycemic band to be calculated.

For further analysis, patients were placed into groups based on the percentage of time spent in certain glycemic bands. Group 1 patients spent the majority of time with SGVs between 80 and 110 mg/dL. Group 2 patients spent the majority of time with SGVs greater than 200 mg/dL.

Statistical analysis was performed on SPSS version 12.0 software (Chicago, Ill). Baseline data are presented as percentages or means with standard deviations. Glucose values were compared at specific intervals postoperatively with a paired *t* test. The Student

TABLE 2. Operative course

Cardiopulmonary bypass time, min	242.5 ± 54.3
Aortic crossclamp time, min	139.1 ± 41.8
Circulatory arrest, n (%)	35 (38)
Circulatory arrest time, min*	17.7 ± 17.3
Regional low-flow perfusion, n (%)	11 (12)
Medications administered during cardiopulmonary bypass	
Steroids, n (%)	70 (75)
Phenoxybenzamine, n (%)	74 (80)

*Only for patients requiring circulatory arrest.

TABLE 3. Summary of adverse events

Type of adverse event	n (%)
Noncardiac	
Infection	17 (18)
Renal insufficiency (creatinine increase >0.5 mg/dL)	11 (12)
Intravascular/intracardiac thrombus	7 (8)
Seizure/stroke	4 (4)
Pleural effusion (requiring treatment)	2 (2)
Cardiac	
Postoperative arrhythmia	8 (9)
Ventricular dysfunction (≥moderate)	2 (2)
Cardiac arrest	2 (2)
Pericardial effusion (requiring treatment)	1 (1)
Pulmonary hypertensive crisis	1 (1)

t test was used to compare AE (yes/no) groups with respect to the percentage of time in each SGV band. Two-by-two contingency tables analysis was used to assess the effect of binary variables on the development of AEs, with results being expressed as odds ratios with 95% confidence intervals. Logistic regression analysis was used to estimate the increase in the odds of development of an AE for continuous variables.

For continuous variables, such as postoperative and cardiovascular intensive care unit (CVICU) length of stay (LOS), group status (ie, group 1 and group 2) was compared with respect to the median by using the Mann–Whitney *U* test. Multiple logistic regression was used to determine whether group status was independently associated with the development of an AE.

The study was approved by the Institutional Review Board of Texas Children's Hospital and Baylor College of Medicine. Individual consent was waived.

Results

Resource Use and AEs

The median CVICU LOS was 6 days (25th–75th percentile, 5–7 days), and the median postoperative LOS was 11 days (25th–75th percentile, 9–14 days). There were 71 AEs (noncardiac, *n* = 57; cardiac, *n* = 14) that occurred in 45 (48%) of 93 patients. A list of common AEs is shown in Table 3. Common AEs included infection (bloodstream, urinary, or respiratory tracheal; *n* = 17), renal insufficiency (serum creatinine increase >0.5 mg/dL from baseline; *n* = 11), cardiac arrhythmia (*n* = 8), and intracaval thrombus, atrial thrombus, or both (*n* = 7).

Preoperative and Postoperative Serum Glycemic Profile

The mean SGV before the ASO was 91 ± 19 mg/dL. Only 1 patient had an SGV of greater than 150 mg/dL. There were 1037 SGVs (11.2 ± 3.1 SGVs per patient) documented in the first 24 postoperative hours. Figure 1 demonstrates the glucose levels for the overall cohort at specific time intervals postoperatively. Immediately postoperatively, SGVs were increased, with a mean of 201 ± 82 mg/dL. The SGVs

Figure 1. Postoperative glucose values. The horizontal lines in the box denote the 25th, 50th, and 75th percentile values. The error bars denote the 5th and 95th percentile values. The 2 symbols below the 5th percentile error bar denote the 0th and 1st percentile values. The 2 symbols above the 95th percentile error bar denote the 99th and 100th percentiles. The square symbol in the box denotes the mean of the column of data.

decreased significantly at each 6-hour interval, with most patients having normal glucose levels by 24 hours postoperatively (mean SGV, 108 ± 38 mg/dL). Figure 2 demonstrates the overall percentage of time spent in each glycemic band and the percentage of time spent in each glycemic band in patients who had and did not have an AE.

Analysis of Serum Glycemic Profile and AEs

Overall, patients spent the least percentage of time with SGVs of less than 80 mg/dL (mean, $3.0\% \pm 6.7\%$) and the most percentage of time with SGVs between 111 and 150 mg/dL (mean, $30.6\% \pm 22.4\%$). AEs were associated with having spent more time with SGVs of less than 80 mg/dL (mean, $4.8\% \pm 8.6\%$ vs $1.4\% \pm 3.6\%$ in those without an AE; *P* = 0.01), more time with SGVs between 80 and 110 mg/dL (mean, $36.4\% \pm 32.2\%$ vs $19.2\% \pm 20.9\%$ in those without an AE; *P* = .03), and less time with SGVs between 111 and 150 mg/dL (mean, $25.1\% \pm 20.6\%$ vs $35.7\% \pm 23.1\%$ in those without an AE; *P* = .03).

The data were also analyzed according to the percentage of time in the first 24 hours spent in specific glycemic bands: group 1 patients (*n* = 23), greater than 50% time with SGVs between 80 and 110 mg/dL; group 2 patients (*n* = 13), greater than 50% of time with SGVs of greater than 200 mg/dL. Baseline and operative characteristics between group 1 and group 2 patients are shown in Table 4.

When compared with the remainder of the cohort, patients in group 1 were more likely to have an all-cause AE

Figure 2. Percentage time spent in specific glycemic bands. The horizontal lines in the box denote the 25th, 50th, and 75th percentile values. The error bars denote the 5th and 95th percentile values. The 2 symbols below the 5th percentile error bar denote the 0th and 1st percentile values. The 2 symbols above the 95th percentile error bar denote the 99th and 100th percentiles. The square symbol in the box denotes the mean of the column of data.

($P = .001$), renal insufficiency ($P < .001$), or an episode of hypoglycemia (SGV < 80 mg/dL, $P = .008$; Table 5). Group 1 patients were also at increased risk of having an AE when compared with group 2 patients ($P = .03$). Common AEs in group 1 patients included renal insufficiency ($n = 8$, 35%), infection ($n = 5$, 22%), and cardiac arrest ($n = 2$, 9%). AEs in group 2 patients included supraventricular tachycardia ($n = 3$, 23%), infection ($n = 1$, 8%), and pulmonary hemorrhage ($n = 1$, 8%). Group 2 patients were not at increased risk for having an AE compared with the rest of the cohort. Group status designation was not associated with duration of mechanical ventilation for more than 48 hours, duration of inotropic support for more than 48 hours, or CVICU LOS beyond 72 hours. Additionally, group status designation was not associated with total duration of mechanical ventilation, inotropic support, CVICU LOS, or postoperative LOS.

By using multivariable analysis and controlling for preoperative factors (gestational age, birth weight, age at ASO, preoperative serum creatinine value, preoperative glucose value, preoperative balloon atrial septostomy, preoperative inotropes, anatomic descriptors [cardiac diagnosis and coronary artery anatomy], intraoperative course [cardiopulmonary bypass and aortic crossclamp times], steroid administration during cardiopulmonary bypass, and phenoxybenzamine administration) and postoperative hypoglycemia, being a patient in group 1 was determined to be independently associated with an AE (adjusted odds ratio, 13.7; 95% confidence interval, 2.3–83.0; $P = .004$).

Discussion

We have described in detail the range of SGVs encountered in infants after the ASO. Only 23% of patients spent the majority of time with tight glucose control (80–110 mg/dL), as defined by prior studies from adult intensive care patients.⁷ Importantly and in contrast to adult patients, the patients in our study who spent the majority of time with tight glucose control had an increase in the number of AEs. This risk for morbidity was also independent of other known risk factors, including gestational age, birth weight, cardiopulmonary bypass time, and preoperative condition.

Additionally, patients who spent the majority of time with the highest SGVs (> 200 mg/dL) were not at increased risk for AEs. The reason for this is not entirely clear. One potential explanation is that hyperglycemia is part of the normal response to the stress of cardiac operations,¹⁹ which is mediated in part by increased cortisol, inflammatory cytokines, catecholamine values, and insulin resistance.²⁰ Neonates not exhibiting hyperglycemia after cardiac operations might have an impaired ability to mount an appropriate stress response, thereby placing these infants at increased risk for morbidity. Whether lack of a hyperglycemic response is associated with an impaired adrenal axis or cortisol insufficiency was not addressed in this study. However, this would be an important avenue of future inquiry and is a focus of investigation at our institution.

This study is in contrast to the other pediatric study that has evaluated hyperglycemia as a risk factor for AEs in

TABLE 4. Baseline and operative characteristics by group designation

Factor	Group 1 (n = 23)	Group 2 (n = 13)	P value
Demographic data			
Gestational age, wk	38.7 ± 1.6	37.9 ± 1.4	.19
Age at operation, wk	3.6 ± 8.4	1.5 ± 1.2	.38
Birth weight, kg	2.8 ± 1.6	2.9 ± 0.9	.90
Weight at operation, kg	3.8 ± 1.3	3.2 ± 0.3	.03
Anatomic descriptors			
D-TGA with IVS, n (%)	12 (52)	5 (38)	.50
D-TGA with VSD, n (%)	7 (30)	7 (53)	.29
Taussig–Bing anomaly, n (%)	4 (17)	1 (8)	.64
Yacoub type A coronary arteries, n (%)	17 (74)	8 (62)	.48
Yacoub type D coronary arteries, n (%)	3 (13)	2 (15)	1.0
Single coronary artery, n (%)	3 (13)	2 (15)	1.0
Preoperative interventions			
Intubated preoperatively, n (%)	9 (39)	3 (23)	.47
Balloon atrial septostomy, n (%)	17 (74)	10 (77)	1.00
Inotropes, n (%)	7 (30)	0 (0)	.04
Prostaglandin discontinued before ASO, n (%)	10 (43)	9 (69)	.18
Operative course			
Cardiopulmonary bypass time, min	246.9 ± 63.0	269.1 ± 71.1	.34
Aortic crossclamp time, min	148.0 ± 50.8	157.4 ± 57.1	.61
Circulatory arrest, n (%)	10 (43)	8 (62)	.49
Circulatory arrest time, min*	18.1 ± 16.1	9.5 ± 5.2	.17
Regional low-flow perfusion, n (%)	6 (26)	2 (15)	.68
Steroids, n (%)	15 (65)	10 (77)	.43
Phenoxybenzamine, n (%)	19 (83)	11 (85)	1.00

D-TGA, Dextro-transposition of the great arteries; IVS, intact ventricular septum; VSD, ventricular septal defect; ASO, arterial switch operation. *Only for patients who required circulatory arrest.

postoperative cardiac patients. In the study by Yates and associates,²¹ postoperative hyperglycemia was found to be associated with increased AEs in an older patient population undergoing a variety of cardiac operations. This study only looked at the maximum SGV per day in the postoperative period. As is evidenced by Figure 1 of our study, the SGVs are highly variable over the first 24 hours postoperatively, and evaluating only one point in time will not likely accurately reflect the true physiologic state.

There were several other important differences between our study and the study by Yates and associates.²¹ Almost the entire cohort in our study had normal or only mildly increased SGVs 24 hours after their operations, which is in contradistinction to the several days of hyperglycemia noted by Yates and associates. Additionally, the mortality rate in our study was 1% compared with the 11% reported by Yates and associates. Also, our study only included infants, who might be more susceptible to AEs caused by hypoglycemia. These differences in the patient population between the studies might help in part to explain the different findings.

These findings are similar to those of de Ferranti and co-workers,¹⁰ who noted that short-term hyperglycemia did not predict AEs but periods of hypoglycemia during periods of stress were disadvantageous. In their study intraoperative hyperglycemia was not associated with long-term neurodeve-

lopmental outcome but did predict a more rapid normalization of the electroencephalogram. Short periods of hypoglycemia intraoperatively, however, were associated with more electroencephalographic seizures.

There are several limitations to our study. It is a retrospective study from a single center, and the findings might not be applicable to other centers and other populations. Additionally, SGVs were not controlled with insulin, which might have affected the development of AEs. Insulin has been associated with an anti-inflammatory effect²² and has been demonstrated to maintain hepatic mitochondrial ultrastructure,²³ which could be beneficial in critically ill patients. However, in the study by Finney and colleagues,¹⁸ the primary benefit of insulin therapy was glycemic control and not a beneficial effect from insulin administration. Increased insulin administration in the same study was actually associated with increased mortality.

Which critically ill pediatric patients would potentially benefit from insulin therapy to achieve tight glucose control? This is an important and still unanswered question. This is a crucial point because there might be a tendency to adopt therapies used successfully in adult patients to children before the safety and efficacy of the therapy has been established. This issue is highlighted by the recent pediatric activated protein C (APC) trial. The trial, which evaluated the use of APC in patients with sepsis, was halted

TABLE 5. Factors associated with adverse events

Factor	Odds ratio	95% CI	P value
All-cause adverse events			
Group 1	5.7	1.9–17.3	.001
Group 2	0.6	0.2–2.1	.55
Birth weight, kg	1.2	0.9–1.7	.31
Gestational age, wk	0.9	0.7–1.2	.56
Age at operation, wk	1.0	0.9–1.1	.38
PGE at time of operation	1.5	0.65–3.3	.36
Preoperative inotropes	2.9	1.0–8.0	.04
Single coronary artery	1.9	0.4–8.4	.48
Steroids on CPB	0.5	0.2–1.5	.22
Phenoxybenzamine	0.8	0.3–2.2	.60
CPB time, min	1.0	0.9–1.1	.09
Aortic crossclamp time, min	1.0	0.9–1.0	.17
Circulatory arrest time, min*	1.1	0.9–1.1	.08
Renal insufficiency			
Group 1	11.9	2.8–50.3	<.001
Group 2	†	†	.35
Birth weight, kg	2.6	0.8–8.6	.12
Gestational age, wk	0.8	0.6–1.1	.15
Age at operation, wk	1.0	0.8–1.1	.76
PGE at time of operation	0.6	0.2–2.1	.53
Preoperative inotropes	1.2	0.3–4.9	1.00
Single coronary artery	1.1	0.1–9.6	1.0
Steroids on CPB	0.2	0.1–0.7	.01
Phenoxybenzamine	2.5	0.3–21.0	.35
CPB time, min	1.0	0.9–1.1	.66
Aortic crossclamp time, min	1.0	0.9–1.0	.99
Circulatory arrest time, min*	1.0	0.9–1.1	.99
Hypoglycemia (any serum glucose value <80 mg/dL)			
Group 1	3.7	1.4–9.9	.008
Group 2	0.7	0.2–2.6	.75
Birth weight, kg	2.2	0.9–5.2	.06
Gestational age, wk	1.2	0.9–1.6	.23
Age at operation, wk	1.0	0.9–1.1	.41
PGE at time of operation	0.9	0.4–2.2	.80
Preoperative inotropes	0.8	0.3–2.4	.75
Single coronary artery	0.3	0.1–2.6	.43
Use of steroids on CPB	0.6	0.2–1.6	.27
Use of phenoxybenzamine	1.0	0.3–3.2	.98
CPB time, min	0.9	0.9–1.1	.49
Aortic crossclamp time, min	1.0	0.9–1.0	.17
Circulatory arrest time, min*	1.0	0.9–1.0	.97

CI, Confidence interval; PGE, prostaglandin E; CPB, cardiopulmonary bypass. *Only for patients who had circulatory arrest. †No patients had renal insufficiency.

prematurely by the US Food and Drug Administration and Eli Lilly after the external data-monitoring committee noted a lack of effectiveness of APC and an increase in the number of central nervous system hemorrhages in patients administered APC.²⁴

In our study patients with the lowest glucose levels had more AEs, whereas those who spent the most time with mild hyperglycemia (SGV, 111–150 mg/dL) fared better. It

is not clear that this population would benefit in any way from insulin therapy to keep SGVs within a tight range, and conversely, there would be the real risk of inducing harm.

Conclusions

In contrast to adult critically ill patients, hyperglycemia does not appear to be detrimental in postoperative infants with congenital heart disease. Patients who spent the majority of the first postoperative day with SGVs between 80 and 110 mg/dL were more likely to have periods of hypoglycemia and AEs. Further investigation is warranted to define the optimal glucose level in this patient population, and following the adult guidelines for glucose control is not warranted at this time.

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