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Tight glycemic control with insulin does not affect skeletal muscle degradation during the early post-operative period following pediatric cardiac surgery

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Abstract

Objective—Critical illness is associated with significant catabolism and persistent protein loss correlates with increased morbidity and mortality. Insulin is a potent anti-catabolic hormone; high-dose insulin decreases skeletal muscle protein breakdown in critically ill pediatric surgical patients. However, insulin's effect on protein catabolism when given at clinically utilized doses has not been studied. The objective was to evaluate the effect of post-operative tight glycemic control and clinically-dosed insulin on skeletal muscle degradation in children after cardiac surgery with cardiopulmonary bypass.

Design—Secondary analysis of a two-center, prospective randomized trial comparing tight glycemic control with standard care. Randomization was stratified by study center.

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Patients—Children 0-36 months who were admitted to the ICU after cardiac surgery requiring cardiopulmonary bypass.

Interventions—In the tight glycemic control (TGC) arm, insulin was titrated to maintain blood glucose between 80-110 mg/dL. Patients in the control arm received standard care. Skeletal muscle breakdown was quantified by a ratio of urinary 3-methylhistidine to urinary creatinine (3MH:Cr).

Main Results—A total of 561 patients were included: 281 in the TGC arm and 280 receiving standard care. There was no difference in 3MH:Cr between groups (TGC 249 ± 127 vs. standard care 253 ± 112, mean ± standard deviation in μmol/g, P=0.72). In analyses restricted to the TGC patients, higher 3MH:Cr correlated with younger age as well as lower weight, weight-for-age z-score, length, and body surface area (P<0.005 for each), and lower post-operative day 3 serum creatinine (r=-0.17, P=0.02). Sex, prealbumin, and albumin were not associated with 3MH:Cr. During urine collection, 245 patients (87%) received insulin. However, any insulin exposure did not impact 3MH:Cr (t-test, P=0.45), and there was no dose-dependent effect of insulin on 3MH:Cr (r=-0.03, P=0.60).

Conclusion—Though high-dose insulin has an anabolic effect in experimental conditions, at doses necessary to achieve normoglycemia, insulin appears to have no discernible impact on skeletal muscle degradation in critically ill pediatric cardiac surgical patients.

Keywords

Tight glycemic control; critical illness; children; proteolysis; catabolism; insulin

Introduction

The physiologic response to trauma and critical illness results in significant catabolism(1-3). The persistent negative nitrogen balance that follows is associated with impaired respiratory function, increased risk of infection, deficient wound healing, prolonged recovery time, and increased mortality(4-6). Neonates who undergo repair of congenital heart disease have substantial proteolysis and negative nitrogen balance with a peak during the first post-operative day(7). Though adequate nutritional provision improves nitrogen balance in critically ill patients, it appears to do so by increasing protein synthesis rather than minimizing protein loss, and does not completely reverse catabolism(3,8).

Tight glycemic control has been evaluated as a potential therapy for critically ill patients. Aggressive blood glucose control has been studied for its potential to decrease morbidity and mortality in critically ill adults with mixed results(9-11). Its benefit for children is even less clear(12-15). Control of hyperglycemia in burn and oncology patients improves skeletal muscle metabolism, which may contribute to improved outcomes(16-18). The effect of tight glycemic control on skeletal muscle protein breakdown has not been studied in critically ill children.

A variety of potential anabolic agents and strategies have been employed in the attempt to improve nitrogen balance in critical illness including growth hormone, insulin-like growth factor-1, and testosterone analogs(19-21). Under experimental circumstances, insulin is a

potent anabolic hormone that significantly inhibits cellular mechanisms that lead to skeletal muscle degradation(22). Using a hyperinsulinemic-euglycemic clamp, high doses of insulin decrease whole-body protein breakdown in critically ill children(23). However, the independent effect of lower, clinically indicated doses of insulin (i.e., amounts needed to treat hyperglycemia) on protein breakdown has not been evaluated in severely ill patients.

Thus, the aims of this investigation were to use the urinary 3-methylhistidine to creatinine ratio to evaluate the effect of post-operative tight glycemic control versus standard care on skeletal muscle degradation and to study the independent effect of insulin on skeletal muscle degradation in children during the first day after cardiac surgery with cardiopulmonary bypass (the maximal metabolic flow phase).

Materials and Methods

This study was performed as part of a two-center randomized trial conducted at Boston Children's Hospital and the University of Michigan C.S. Mott Children's Hospital [the Safe Pediatric Euglycemia after Cardiac Surgery trial](24). The SPECS trial aimed to test the hypothesis that tight glycemic control would decrease infection rates in children admitted to the cardiac intensive care unit (ICU) after cardiac surgery. Children 0-36 months admitted to the cardiac ICU following cardiac surgery with cardiopulmonary bypass were included. Those with diabetes or insufficient vascular access were excluded. The institutional review boards at each center approved this trial and written informed consent was obtained from parents or legal guardians.

Patients randomized to the tight glucose control (TGC) arm received regular human insulin at the lowest sufficient dose to keep blood glucose between 80 to 110 mg per deciliter. Both groups had continuous glucose monitoring (Guardian REAL-Time device, Medtronic Diabetes, Northridge, CA) for the first 3 days post-operatively. The SPECS trial found no difference in the number of health care-associated infections (pneumonia, bloodstream, urinary tract, and surgical-site) per 1,000 cardiac ICU days between the TGC and standard care groups(24). In a secondary analysis, patients were stratified by RACHS-1 (Risk Adjustment in Congenital Heart Surgery) category, which reflects mortality associated with a patient's specific operative procedure(25,26).

Study Design

The current study was planned *a priori* as part of the SPECS trial and all of the children enrolled had urine samples collected for this analysis. Randomization was stratified by study center. During the study period, quantitative urinary 3-methylhistidine (3MH) and creatinine (Cr) assays could routinely be obtained only at Boston Children's Hospital, thus analysis was limited to the patients enrolled at Boston. Since the second aim of this investigation was to evaluate the effect of insulin on skeletal muscle breakdown, analysis for this aim was limited to children in the TGC arm of the study. Since not all of the patients in the TGC group received insulin, comparison between the groups is not a clear reflection of the independent effect of insulin. Subjects missing urinary 3MH and/or urinary Cr were excluded from analysis.

Quantification of Skeletal Muscle Degradation

The majority of the protein lost during the flow phase of critical illness is from skeletal muscle, which acts as a metabolic reservoir, producing energy and free amino acids for use by the critical organs(27). Urinary 3MH is a robust biomarker of skeletal muscle breakdown(3, 28, 29). 3MH is formed by the post-translational methylation of specific histidine residues in the myofibrillar proteins actin and myosin and is released when these proteins undergo proteolysis(30,31). Because it is not capable of charging tRNA, it is not reutilized for protein synthesis and is quantitatively excreted in the urine(2,32). It is not present in cardiac myosin(33). Major surgery results in increased loss of body nitrogen and an increase in the excretion of 3MH, which correlates with whole body proteolysis(2, 28, 29). Therefore, in this study, urinary 3MH was chosen as the primary outcome variable because it is a biomarker of skeletal muscle breakdown. Urinary 3MH is normalized to whole-body muscle mass using urinary Cr in patients with intact renal function(34). It is thus expressed as a ratio: urinary 3MH:Cr. For reference, one study found a mean 3MH:Cr of 148 μmol/g for healthy premature neonates(35).

Sample Collection and Analysis

Urine was collected from the time of post-operative admission into the cardiac ICU until the urinary catheter was removed. Patients who were anuric were excluded. All urinary 3MH concentrations were measured using an Agilent/HP6890 gas chromatographer/mass spectrometer in a single lab according to previously published procedures(36). Urinary creatinine was quantified using standard methods by the clinical laboratories at the participating institutions. Serum creatinine, prealbumin, and albumin concentrations for each patient were only available from post-operative day 3 of the trial (preoperative studies were not available).

Statistical Analysis

Patient characteristics were compared between treatment groups using t-tests for continuous variables and Fisher's exact tests for categorical variables. The associations between patient characteristics and 3MH:Cr were assessed using t-tests for binary variables and Pearson correlations for continuous variables, limited to the TGC group. Partial Pearson correlations adjusting for RACHS-1 category (1-2 vs. ≥3 or not assignable) were performed to further explore the associations between patient age/size variables and 3MH:Cr. Statistical and graphical analyses were performed with the use of SAS (version 9.3) and PASW Statistics (version 18). Weight-for-age z-scores were calculated based on the World Health Organization (WHO) child growth standards using the “Igrowup_restricted” SAS macro available at www.who.int/childgrowth/software/en. Given the sample sizes used in these analyses, with a two-sided 0.05-level t-test we have 84% power to detect a treatment group difference in 3MH:Cr of 0.25 standard deviation units (e.g., a 25-unit difference if the standard deviations were equal to 100).

Results

A total of 648 patients were enrolled at Boston Children's Hospital. Of these patients, 561 had adequate urine sample collections and were included in this analysis. Of the 561 studied

here, 281 were randomized to the TGC arm and 280 received standard care. Patient characteristics are listed in Table 1. Urine was collected for 21.5 ± 5.6 hours (mean ± standard deviation) from the time of cardiac ICU admission. No patients in the standard care group were treated with insulin during urine collection. By protocol, patients did not receive substantial enteral or parenteral nutrition during the first post-operative day; specific measurements were not obtained. Of the 446 patients still on study on post-operative day 2, a subset received some enteral nutrition (n=198, 44%) and parenteral nutrition (n=39, 9%). There were more hypoglycemic events in the TGC group compared to the standard care group (P<0.001), but only a marginally significant difference in severe hypoglycemic episodes between groups (P=0.07). The mean urinary 3MH:Cr was 251 μmol/g (standard deviation 119) across the TGC and standard care groups, and there was no difference in 3MH:Cr between groups (Figure 1, P=0.72).

To evaluate the independent effect of insulin on 3MH:Cr, analysis was limited to the 281 patients in the TGC group. Factors potentially influencing 3MH:Cr are shown in Tables 2 and 3. Younger age, lower weight, lower weight-for-age z-score, shorter length, smaller body surface area, absence of prematurity, and lower post-operative day 3 serum creatinine correlated with higher 3MH:Cr (P≤0.02 for each). Post-operative day 3 albumin and prealbumin levels were not associated with 3MH:Cr. 3MH:Cr was not different in the insulin exposed versus non-exposed groups (P=0.45). Figure 2 shows total insulin received during urine collection plotted against 3MH:Cr. Of the 245 TGC patients who had insulin, the median dose was 0.37 units/kg (interquartile range 0.18-0.65). There was no correlation between these values (r=-0.03, P=0.60), and thus no dose-dependent effect of insulin on 3MH:Cr.

In the TGC group, having a higher RACHS-1 category (≥3 or not assignable vs. 1-2) was associated with younger age and lower weight, length, and body surface area (t-tests, P≤0.03 for each). However, adjusting for RACHS-1 category did not appreciably change the statistically significant correlations between patient age, weight, length, and body surface area with 3MH:Cr.

Discussion

In this large trial, neither tight glycemic control nor clinically-dosed insulin had an independent effect on the rate of skeletal muscle degradation during the first post-operative day in children undergoing major cardiac operations. Protein loss is the hallmark of the metabolic stress response and persistent negative nitrogen balance is associated with increased morbidity and mortality(4-6). Neonates and young children are at particularly high risk given their limited reserves(37). Hence preventing protein degradation is essential to optimizing outcomes for critically ill pediatric patients. However, the most effective therapy to stem such catabolism remains unclear. Infants with congenital heart disease who undergo cardiac repair have substantial negative nitrogen balance and skeletal muscle loss (reflected by high urinary 3MH:Cr), which is reflected clinically by a high rate of failure to thrive(7). Thus infants undergoing cardiac operations are an ideal group to study when trying to understand these phenomena. The 3MH:Cr levels in this study overall were similar to those

in other published cohorts of children undergoing cardiac operations, and substantially higher than well neonates(7,35).

Experimentally, high dose insulin appears to have an anabolic effect in neonates requiring extracorporeal membrane oxygenation (ECMO), another group known to undergo massive catabolism and protein loss, as well as in healthy adults(38,39). In these studies, however, a hyperinsulinemic-euglycemic clamp was used to provide supra-physiologic doses of insulin (infusion of 0.6 units/kg/hour) while maintaining euglycemia(38). Further, burned rats have decreased levels of proteolysis in response to insulin administration(22). The current investigation is the first to evaluate the effect of low doses of insulin used clinically to control hyperglycemia on protein degradation in critically ill pediatric patients.

Insulin exposure was not associated with a reduction in urinary 3MH:Cr and the total amount of insulin delivered did not correlate with 3MH:Cr in this cohort. The reasons for the absence of an observed effect are not immediately clear from evaluating the collected data. In animal models, the mechanism of the anti-catabolic effect of insulin is related to inhibition of the ubiquitin-proteasome system, which is involved in muscle breakdown(40-42). One molecular study in rats demonstrated that this inhibitory effect of insulin is minimal until the concentration of insulin surpasses a threshold(43). Thus, one potential conclusion would be that insulin given at relatively low doses is insufficient to prevent significant degradation of skeletal muscle because the insulin concentration is insufficient to block this pathway.

One alternative explanation is that the provision of nutrition was inadequate to alleviate skeletal muscle loss. In the current investigation, patients received no nutrition for a period preoperatively and dextrose containing fluids at most for the first post-operative day. Though some patients received enteral or parenteral nutrition by the end of the second day, the total protein and energy allotments prior to the completion of urine collection were not available for analysis, it should be noted that the urine collection period was completed before the end of the second day for most patients. Thus the effect on the subgroup that received some protein could not be evaluated. Nonetheless, the overall protein provision during the study period was poor and hence this essential cofactor for muscle protein preservation was likely lacking in this group. The first post-operative day was chosen for study because this is the interval during which protein loss appears to be at a maximum in this patient population(7, 44). Despite the lack of effect during the acute phase (<1 day after insult), it is possible that insulin administration during the convalescent phase of illness (which was not studied here) could preserve skeletal muscle. It is also possible that patients who were most ill following surgery had both a greater degree of proteolysis and were more insulin-resistant and thus received more insulin. In this case, the possible protein-preserving effect of insulin may have balanced the higher degree of catabolism.

Younger age, and lower weight, length, and body surface area were associated with higher 3MH:Cr in this cohort. Children who require more complex operations are at greater risk of morbidity in the post-operative period(45). The RACHS-1 classification system is a consensus-based tool for categorizing operations by complexity (category 1 = lowest risk, category 6 = highest risk). In this group, younger and smaller patients were generally in

higher RACHS-1 categories than older and larger patients. Thus, these closely associated anthropometric variables likely described a population requiring more complex operations with greater post-operative illness severity and subsequently higher rates of skeletal muscle breakdown.

The etiology of the relationship identified between prematurity and 3MH:Cr is less clear though selection bias may have been a factor; it is possible that some premature infants with significant cardiac disease were not stable enough to undergo major operations and thus the cohort of premature infants included may have been physiologically well compared with children born at term. It is also unclear why patients with higher serum creatinine on day 3 had lower urinary 3MH:Cr, but 3MH and creatinine may have different rates of clearance in those with poor renal function. Alternatively, higher serum creatinine could lead to higher urinary creatinine, which would decrease 3MH:Cr.

This study was limited by the short duration of observation. Though the SPECS trial followed patients through their hospital course, urine collection stopped when urinary catheters were removed (most within 24 hours). This window may have been insufficient to capture an effect of insulin. The significant catabolism associated with cardiac surgery would seem to make this an ideal population in whom to study an effect of low-dose insulin(23). The doses of insulin required in most patients here were relatively low as compared with those given in critically ill adults, thus it is difficult to extrapolate meaning for these results over a broader population(10). The exclusion of data from one of the two centers also limited this investigation.

Conclusion

Despite the anabolic effects of high-dose insulin seen under some experimental conditions, in this large study of children undergoing major cardiac operations, clinically dosed insulin did not decrease skeletal muscle catabolism over the first post-operative day. Unlike in certain populations of adults, tight glycemic control was also not associated with decreased skeletal muscle loss(17,18). Further study may be required for patients receiving high dose insulin and a longer duration of observation may be warranted for pediatric populations with ongoing catabolism.

In summary, this investigation of pediatric cardiac surgery patients suggests that neither insulin administration nor tight glycemic control independently preserves skeletal mass.

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Abbreviations

TGC	tight glycemic control
3MH	3-methylhistidine
3MH:Cr	3-methylhistidine to creatinine ratio

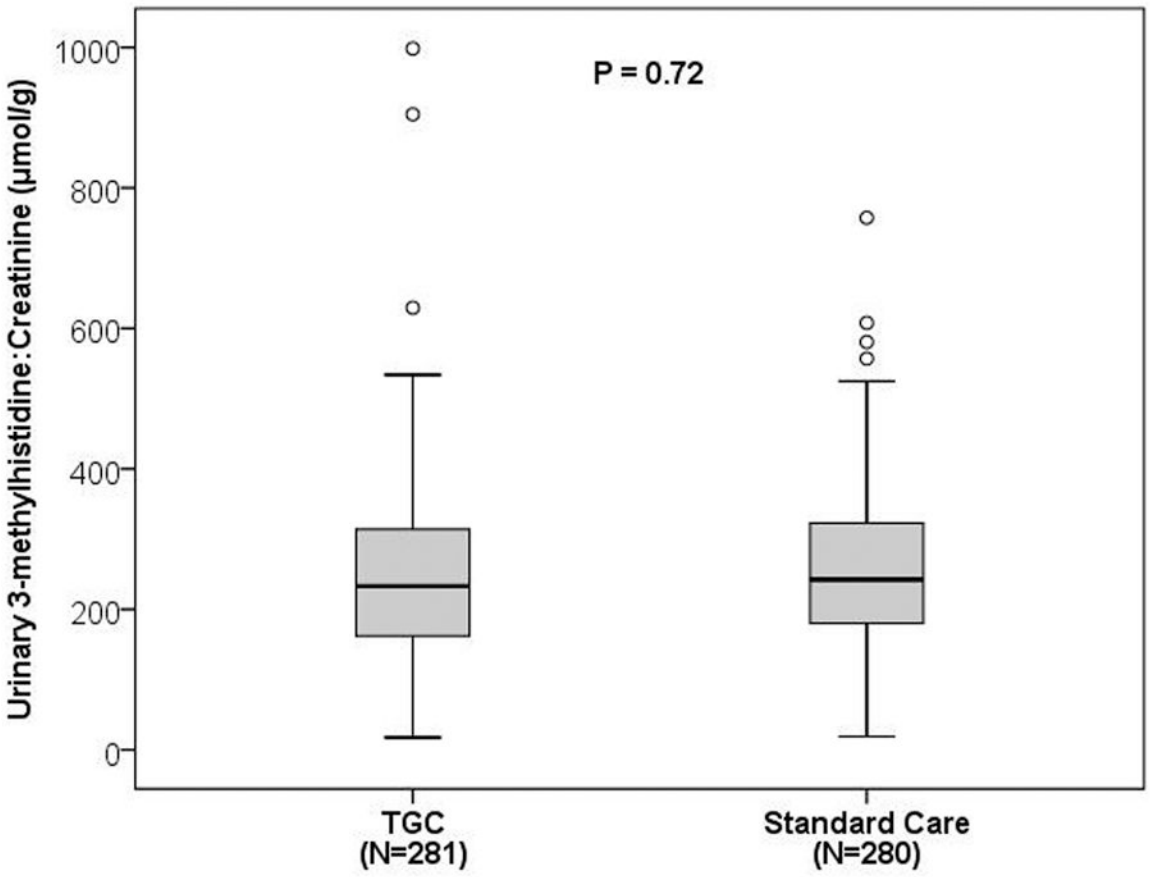

Figure 1.

Urinary 3-methylhistidine:creatinine by treatment group. TGC, tight glycemic control. The boxes represent the interquartile ranges (25th percentile to 75th percentile), while the lines through the boxes represent the medians. The whiskers extend to 1.5 times the height of the box (or, if no case has a value in that range, to the minimum or maximum values), with circles representing outliers. The P value for the comparison between treatment groups was determined by a t-test.

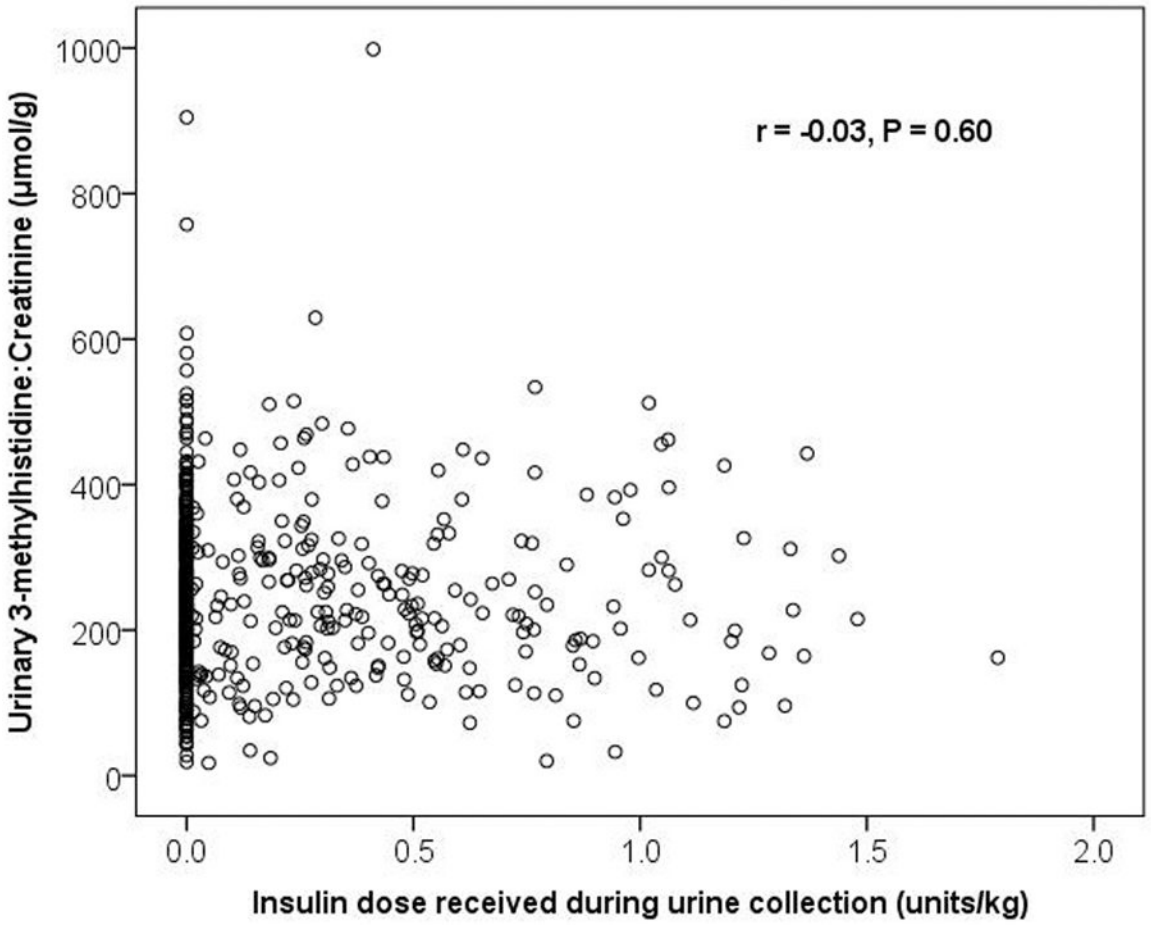

Figure 2.

Urinary 3-methylhistidine:creatinine vs. insulin dose received during urine collection in tight glycemic control patients (N=281). Among the 245 patients who received insulin during urine collection, Pearson correlation r=-0.02, P=0.81.

Table 1

Patient characteristics by treatment group[a]

	Tight Glycemic Control (N=281)	Standard Care (N=280)	P Value[b]
Baseline characteristics			
Age at surgery (mo)	8.0 ± 8.9	8.0 ± 8.4	0.97
Female sex	136 (48)	128 (46)	0.55
Preoperative weight (kg)	6.2 ± 2.8	6.4 ± 2.8	0.39
Weight-for-age z-score	-1.6 ± 1.5	-1.4 ± 1.5	0.10
Preoperative length (cm)[c]	64 ± 13	65 ± 12	0.43
Body surface area (m^2)[c]	0.32 ± 0.11	0.32 ± 0.10	0.42
RACHS-1 category			0.71
1	18 (6)	17 (6)	
2	120 (43)	128 (46)	
3	95 (34)	84 (30)	
4	26 (9)	26 (9)	
5-6	14 (5)	11 (4)	
Not assignable	8 (3)	14 (5)	
RACHS-1 category ≥3 or not assignable	143 (51)	135 (48)	0.55
Premature birth[c]	42 (15)	40 (14)	0.90
Chromosomal anomaly	55 (20)	57 (20)	0.83
Noncardiac structural abnormality	34 (12)	46 (16)	0.15
Post-operative day 1 characteristics			
Initial post-operative blood glucose (mg/dL)	149 ± 52	144 ± 52	0.24
Treated with insulin therapy during urine collection	245 (87)	0	<0.001
Insulin dose received during urine collection (units/kg)[d], median (interquartile range)	0.37 (0.18-0.65)	-	-
Urinary 3-methylhistidine:creatinine (μmol/g)	249 ± 127	253 ± 112	0.72
Mechanically ventilated at the start of post-operative day 2[e]	199 (71)	197 (70)	0.93
Post-operative day 3 labs[f]			
Serum creatinine (mg/dL)	0.37 ± 0.18	0.35 ± 0.18	0.36
Prealbumin (mg/dL)	11.1 ± 3.1	11.1 ± 2.7	0.99
Albumin(g/dL)	3.2 ± 0.5	3.2 ± 0.4	0.74
Adverse events			
ECMO support (during surgery or CICU stay)	8 (3)	7 (3)	1.0
Cardiopulmonary resuscitation (during CICU stay)	6 (2)	5 (2)	1.0
Hypoglycemia			
Severe (<40 mg/dL)	7 (2)	1 (<1)	0.07
Any (<60 mg/dL)	53 (19)	22 (8)	<0.001

[a] Data are mean ± standard deviation or number (percent) unless otherwise specified. CICU, cardiac intensive care unit; ECMO, extracorporeal membrane oxygenation; RACHS-1, Risk Adjustment in Congenital Heart Surgery; TGC, tight glycemic control.

[b] P values for the comparison between treatment groups were determined by t-tests for continuous variables and Fisher's exact tests for categorical variables.

[c] Preoperative length, body surface area, and premature birth available for 280 TGC and 280 standard care patients.

[d] Insulin dose for the 245 TGC patients who received insulin during urine collection.

[e] Post-operative day 2 was the first full day after surgery, starting at 07:00 the morning after post-operative CICU admission and continuing until 06:59 the following morning.

[f] Serum creatinine, prealbumin, and albumin were only available on post-operative day 3 and some subjects were discharged from the CICU before day 3. For these variables the number of patients included and the normal ranges were: serum creatinine: 178 TGC, 171 standard care, 0.3-1.0 mg/dL; prealbumin: 166 TGC, 163 standard care, 12-30 mg/dL; albumin: 168 TGC, 164 standard care, 3.0-4.6 g/dL.

Table 2

Univariate analysis of the effect of binary patient characteristics on urinary 3-methylhistidine:creatinine (3MH:Cr) for TGC patients (N=281)[a]

Patient characteristic	Yes	No	P Value[b]
	Urinary 3-methylhistidine:creatinine		
Female sex	246 ± 117 (136)	253 ± 136 (145)	0.66
RACH-1 category ≥3 or not assignable	251 ± 147 (143)	248 ± 102 (138)	0.88
Premature[c]	206 ± 95 (42)	257 ± 131 (238)	0.02
Chromosomal anomaly	258 ± 148 (55)	247 ± 122 (226)	0.59
Noncardiac structural abnormality	268 ± 163 (34)	247 ± 121 (247)	0.37
Treated with insulin therapy during urine collection	247 ± 123 (245)	264 ± 155 (36)	0.45
Mechanically ventilated at the start of post-operative day 2	249 ± 137 (199)	252 ± 99 (82)	0.85
ECMO support (during surgery or CICU stay)	317 ± 271 (8)	247 ± 121 (273)	0.13
Cardiopulmonary resuscitation (during CICU stay)	339 ± 284 (6)	247 ± 122 (275)	0.08
Severe hypoglycemia (<40 mg/dL)	274 ± 176 (7)	249 ± 126 (274)	0.60
Any hypoglycemia (<60 mg/dL)	252 ± 188 (53)	249 ± 109 (228)	0.87

[a] Data are mean ± standard deviation (number of patients). CICU, cardiac intensive care unit; ECMO, extracorporeal membrane oxygenation; RACHS-1, Risk Adjustment in Congenital Heart Surgery; TGC, tight glycemic control.

[b] P-values for the comparison between categories were determined by t-tests.

[c] Premature available for 280 TGC patients.

Table 3

Univariate analysis of the effect of continuous patient characteristics on urinary 3-methyhistidine:creatinine (3MH:Cr) for TGC patients (N=281)

Patient characteristic	Pearson correlation	P Value
Age at surgery (mo)	-0.19	0.002
Preoperative weight (kg)	-0.21	<0.001
Weight-for-age z-score	-0.19	0.002
Preoperative length (cm)[a]	-0.17	0.005
Body surface area (m^2) [a]	-0.19	0.001
Insulin dose received during urine collection (units/kg)	-0.03	0.60
Post-operative day 3 labs[b]		
Serum creatinine (mg/dL)	-0.17	0.02
Prealbumin (mg/dL)	-0.07	0.38
Albumin (g/dL)	0.05	0.56

[a] Preoperative length and body surface area available for 280 TGC patients.

[b] Labs were only available on post-operative day 3 and some subjects were discharged from the CICU before day 3. Serum creatinine, prealbumin, and albumin available for 178, 166, and 168 TGC patients, respectively.