High Incidence of Insulin Resistance and Dysglycemia Amongst Nondiabetic Cardiac Surgical Patients

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Background. **Undiagnosed glycometabolic dysfunction is prominent amongst nondiabetic cardiac surgical patients, whereas perioperative dysglycemia is associated with adverse outcomes. This study assessed whether the preoperative level of insulin resistance predicts the degree of perioperative dysglycemia in nondiabetic, normoglycemic cardiac surgical patients.**

Methods. **Twenty-two nondiabetic patients awaiting cardiac operations were assessed for metabolic parameters and whole-body insulin resistance (mean glucose infusion [GINF] rate) using the hyperinsulinemic-euglycemic clamp. Intraoperative and postoperative glucose levels and treatment requirements were analyzed. Linear regression analysis was used to find predictors of baseline, peak intraoperative, and mean postoperative fasting blood glucose (FBG).**

Results. **The mean GINF recorded in nondiabetic, normoglycemic patients was 3.5 ± 1.4 mg/kg/min. The mean peak intraoperative and mean postoperative FBG concentrations were 154.9 ± 34.2 mg/dL (range, 108.1 to 227.0 mg/dL) and 120.7 ± 16.2 mg/dL (range, 100.9 to 154.9 mg/dL), respectively. The GINF correlated inversely with mean peak intraoperative ($r = -0.7$, $p = 0.02$) and mean postoperative FBG ($r = -0.8$, $p = 0.01$). The GINF did not correlate with preoperative FBG levels ($r = 0.3$, $p = 0.4$). Preoperative FBG did not correlate with peak intraoperative ($r = 0.4$, $p = 0.5$) or mean postoperative FBG ($r = 0.5$, $p = 0.3$).**

Conclusions. **Nondiabetic, normoglycemic cardiac surgical patients are highly insulin resistant using the hyperinsulinemic-euglycemic clamp. Preoperative insulin resistance, not FBG, is significantly associated with the development of perioperative dysglycemia. Insulin resistance screening may be useful to identify insulin resistance preoperatively and predict the degree of perioperative dysglycemia in cardiac surgical patients but should be performed with a more appropriate and reproducible test.**

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Type 2 diabetic patients historically have poorer clinical outcomes after cardiac operations compared with nondiabetic patients, including a higher incidence of wound infections, neurologic and renal complications, ischemia, and death [1–4]. Recent studies have demonstrated that prediabetic individuals have the same increased risk for early postoperative death as diabetic patients [5, 6].

An important consequence of abnormal glucose metabolism in cardiac surgical patients is the development of perioperative dysglycemia and its subsequent detrimental impact on postsurgical outcomes. Intraoperative and postoperative hyperglycemia has been demonstrated as an independent predictor for adverse outcomes [5]. Even moderate hyperglycemia (≥120 mg/dL) significantly contributes to morbidity and death after cardiac operations [7]. Observational studies have shown that improved glycemic control or insulin infusion, or both, in diabetic patients undergoing cardiac operations leads to improved in-hospital outcomes [3, 4].

Major surgical trauma leads to stereotypical alterations in glucose metabolism, including stimulation of glucose production and impaired glucose utilization, leading to hyperglycemia [8]. The rapid increase in circulating levels of cortisol, catecholamines, and glucagon in response to injury affects glucose homeostasis and leads to tissue insulin resistance [8, 9]. Intraoperative insulin resistance is associated with increased risk of postoperative complications in cardiac surgical patients, independent of diabetic status [10].

This study investigated how the preoperative level of

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insulin resistance in nondiabetic cardiac surgical patients relates to perioperative glucose homeostasis. We assessed a cohort of nondiabetic, normoglycemic patients awaiting cardiac operations for preoperative levels of insulin resistance using the gold standard hyperinsulinemic-euglycemic clamp technique to test the hypothesis that an individual's preoperative level of insulin resistance will predict the degree of perioperative dysglycemia.

Patients and Methods

Between March 2010 and October 2010, patients scheduled for elective cardiac operations, with no previous history of diabetes or impaired glucose tolerance, were approached and recruited from the Department of Cardiac Surgery at St. Vincent's Hospital, Melbourne. Written consent was provided by 22 patients, and each underwent a preoperative assessment for insulin resistance using the reference standard hyperinsulinemic-euglycemic clamp technique [11].

Exclusion criteria included any untreated malignancy, chronic or acute infections, systemic inflammatory conditions, or significant renal impairment (creatinine $>$ 150 μmol/L). Five patients (1 woman, 4 men) were subsequently excluded from further analysis after 3 recorded fasting blood glucose (FBG) concentrations above the diabetic threshold (126.2 mg/dL [7.0 mmol/L]) and 2 others demonstrated an impaired fasting glucose ($>$ 108.1 mg/dL [$>$ 6.0 mmol/L]).

Dysglycemia was defined in accordance with the World Health Organization (WHO) criteria for impaired fasting glucose (FBG 108 to 126 mg/dL) and diabetes threshold (FBG $\geq$ 126 mg/dL). The lower boundary of perioperative dysglycemia was defined as FBG values of 108 to 126 mg/dL, and the upper boundary was FBG values of 126 mg/dL or more. All studies were conducted in the Endocrine Testing Centre of our institution. Ethical approval for all protocols in this study was obtained from the St. Vincent's Hospital Research Governance Unit.

Hyperinsulinemic-Euglycemic Clamp

After a 10- to 12-hour overnight fast, patients were admitted to the Endocrine Testing Centre at 9.00 AM on a day before admission for the cardiac operation. Anthropometric measurements and blood pressure were recorded. Intravenous cannulas were inserted under local anesthesia into an antecubital vein for blood sampling and the opposite antecubital vein to allow dual infusion of insulin at 40 mU/m^2/min and 25% dextrose solution in water. Actrapid insulin (Novo-Nordisk, Bagsvaerd, Denmark) was diluted to a concentration of 100 mU/mL. At this time insulin was administered as a continuous infusion at the rate of 40 mU/m^2/min for 180 minutes, as previously described [11].

A bedside glucose analyser was used to measure the plasma glucose concentration every 10 minutes after the commencement of the insulin infusion by automated glucose oxidation method (Glucose Analyser 2, Beckman Instruments, Fullerton, CA). A variable infusion of 25% glucose was adjusted based on predictions of required glucose infusion rates using the Oxford Clamp V1.0 computer program. Samples were collected at baseline and from 150 to 180 minutes in 10-minute intervals for determination of steady-state plasma glucose and serum insulin concentrations.

The 40 mU/m^2/min insulin infusion rate achieves a steady-state level of hyperinsulinemia that enables complete suppression of hepatic glucose production. When the steady-state level is reached, the rate of glucose infusion equals the rate of glucose metabolized [11]. The mean amount of glucose metabolized (glucose infusion [GINF] rate) at steady state provides an index of whole-body insulin sensitivity to exogenous insulin.

Additional serum samples were collected from each patient at baseline to measure lipid profile, glycosylated hemoglobin, plasma insulin, and C-peptide. Insulin and glucose samples were immediately placed on ice, centrifuged at 4°C for 3,000 rpm for 10 minutes, and stored at −80° C for later analysis.

Intraoperative Assessment

During the operation, each patient underwent routine arterial blood gas sampling once hourly. Each sample was processed immediately within the operating suite by the attending anesthetist using a GEM Premier 3000 Blood Gas Analyzer (Instrumentation Laboratory, Bedford, MA). The peak intraoperative blood glucose concentration reached during cardiopulmonary bypass was recorded. Intraoperative insulin administration was noted, along with dosage. The protocol for intraoperative glucose management at our institution is to commence an insulin infusion if the intraoperative FBG level exceeds 180.2 mg/dL (10.0 mmol/L). In this situation, a 2-unit to 5-unit bolus is administered, followed by a maintenance dose according to clinical circumstance and treatment response.

Postoperative Assessment

Upon the return of each patient to the cardiothoracic ward from the intensive care unit after the operation, a venous FBG sample was taken each day for an average of 6 days at 7:00 AM until discharge. Any requirements for insulin administration were noted, along with dosage. On the ward, patients were managed according to the hospital protocol for postoperative hyperglycemia; any patients with FBG of 162.2 mg/dL or higher ($\geq$9.0 mmol/L) on two consecutive readings (4 hours apart) were commenced on an insulin infusion of 2 U/h (100 U of Actrapid in 100 mL of 5% glucose) and monitored every 2 hours.

Plasma glucose was measured using a YSI 1500 Sidekick analyser (Yellow Springs Instrument, Yellow Springs, OH), using a glucose oxidase method, interassay coefficient of variation of 2.4%. Serum insulin was measured by radioimmunoassay with dextran-coated charcoal separation of bound and free fractions [12] with less than 1% cross-reactivity to proinsulin (Linco Research, St Louis, MO). The interassay coefficient of variation for this

assay is 9.3% at insulin levels of 3.8 mU/L, 6.7% at 20 mU/L, and 4.9% at 35.4 mU/L. The sensitivity of the assay is 0.6 mU/L.

Whole-Body Insulin Resistance

The index of whole-body insulin resistance (GINF) was derived from the mean glucose infusion rate achieved during steady state (150 to 180 minutes) of each clamp study [11]. This index of insulin resistance was correlated with preoperative FBG, peak intraoperative plasma glucose, and the mean postoperative FBG in each patient. The significance of preoperative FBG as a predictor of perioperative dysglycemia was compared with that of whole-body insulin resistance. Surrogate measures of insulin resistance, the Quantitative Insulin Sensitivity Check Index (QUICKI), measured as (log (FBG) + log (fasting plasma insulin) [13]; fasting insulin [14], homeostasis model assessment of insulin resistance (HOMA-IR; FBG × fasting plasma insulin/22.5) [15], and the triglyceride (TG)/high-density lipoprotein (HDL) ratio [16], were derived from clinical and metabolic variables collected in the 17 study patients and examined for correlation with the GINF as well as the peak intraoperative and mean postoperative FBG concentration.

Statistical analysis was performed using SPSS 17.0 software (SPSS Inc, Chicago, IL). Data were assessed for normality and log-transformed where appropriate. All data are expressed as mean ± standard deviation. Pearson correlation and linear regression were used to examine the relationships between these variables; all analyses were corrected for age and sex. Statistical significance was taken at $p < 0.05$.

Results

The 17 study patients (14 men) were normoglycemic (mean FBG, 97.3 ± 7.2 mg/dL) based on the WHO criteria for normal FBG levels (≤ 108.0 mg/dL). The average age was 60 ± 12 years. All patients included in the study were white. This population displayed a wide range of adiposity, with body mass indexes varying from 23.6 to 36.5 kg/m^2. No patients were receiving pharmacologic therapy known to affect glucose tolerance. The clinical and metabolic characteristics of the study population are reported in Tables 1 and 2.

All recruited patients underwent assessment for whole-body insulin resistance using the gold standard hyperinsulinemic-euglycemic clamp method, where a lower requirement for glucose indicates more insulin resistance. The mean GINF recorded in the patients was 3.5 ± 1.4 mg/kg/min (Table 1). (The mean GINF for nonobese, healthy individuals is 7.0 to 11.2 mg/kg/min [11, 17]). The level of insulin resistance ranged from 1.3 to 6.0 mg/kg/min. The 3 newly diagnosed type 2 diabetic patients (1 woman, 2 men) displayed GINF values of 1.7, 1.5, and 2.2 mg/kg/min, respectively. The 2 men with impaired FBG levels had GINF values of 1.4 and 1.5 mg/kg/min, respectively. These 5 patients were excluded from further analysis. Inclusion of data from these patients did not affect results from the linear regression analysis.

The mean of measured peak intraoperative plasma glucose concentrations was 154.9 ± 34.2 mg/dL (range, 108.1 to 227.0 mg/dL). The mean postoperative FBG concentration recorded in all patients was 120.7 ± 16.2 mg/dL (range, 100.9 to 154.9 mg/dL; Table 1). Two patients required insulin therapy upon return to the car-

Table 1. Patient Metabolic Characteristics

Variable[a]	Male (n = 14)	Female (n = 3)	Total (N = 17)
Body mass index, kg/m^2	28.9 ± 3.9	32.7 ± 4.4	29.8 ± 4.2
Waist circumference, cm	103 ± 12	108 ± 7.5	105 ± 11
FBG, mg/dL	97.3 ± 7.2	98.1 ± 7.3	97.3 ± 7.2
Fasting plasma insulin, mU/L	11.1 ± 7.6	9.1 ± 3.1	10.7 ± 6.9
Fasting C-peptide, pmol/mL	1.1 ± 0.5	0.9 ± 0.3	1.0 ± 0.4
HbA_{1c} %	5.7 ± 0.2	5.6 ± 0.3	5.7 ± 0.3
Blood pressure, mm Hg			
Systolic	131 ± 21	138 ± 3	132 ± 19
Diastolic	77 ± 9	84 ± 4	78 ± 8
Lipid levels, mmol/L			
Total cholesterol	4.5 ± 0.9	4.9 ± 1.6	4.5 ± 1.0
Fasting triglyceride	1.9 ± 0.2	1.6 ± 0.3	1.8 ± 1.1
High-density lipoprotein	1.0 ± 0.3	1.3 ± 0.1	1.1 ± 0.3
GINF, mg/kg/min	3.4 ± 1.3	3.6 ± 2.1	3.5 ± 1.4
Glucose levels, mg/dL			
Peak intraoperative	158.6 ± 32.4 (118.9–227.0)	136.9 ± 45.0 (108.1–189.1)	154.9 ± 34.2 (108.1–227.0)
Mean postoperative	120.7 ± 14.4 (100.9–138.7)	126.1 ± 34.2 (100.9–154.9)	120.7 ± 16.2 (100.9–154.9)

[a] Data expressed as mean ± standard deviation (range) unless otherwise specified.

FBG = fasting blood glucose; GINF = glucose infusion rate; HbA_{1c} = glycosylated hemoglobin.

Table 2. Patient Clinical Characteristics

Variable	Mean ± SD or No. (%)
Age, years	60 ± 12
Coronary artery disease	15 (88)
Diseased vessels, No.	
1	2 (13)
2	2 (13)
3	11 (74)
Valvular disease	6 (35)
Aortic stenosis	4 (67)
Aortic insufficiency	2 (33)
Hypertension	11 (65)
Obesity (BMI ≥ 30 kg/m^2)	9 (53)
Hypercholesterolemia	15 (88)
Previous myocardial infarction	5 (29)
Previous cerebrovascular accident	1 (6)
Heart failure	6 (35)
NYHA functional class	
I	0
II	5 (83)
III	1 (17)
Smoker (active/previous)[a]	8 (47)

[a] Defined > 20 pack years.

BMI = body mass index; NYHA = New York Heart Association; SD = standard deviation.

diothoracic ward after their operation. A 62-year-old man (GINF, 1.3 mg/kg/min) required 3 U/h of insulin on day 1 and 2 of his postoperative ward stay. A 78-year-old man (GINF, 2.0 mg/kg/min) required 4 U/h on day 1. Neither patient received glycogenic (including noradrenaline, adrenaline, glucocorticosteroid) drug therapy during his intensive care unit stay. Daily FBG measurements recorded on the days of insulin administration were excluded from the final analysis. No carbohydrate exposure occurred at the time of the daily FBG test because no patient received dextrose-containing maintenance fluids.

The level of whole-body insulin resistance, as measured by the hyperinsulinemic-euglycemic clamp (GINF), displayed a close, inverse correlation with the peak intraoperative plasma glucose concentration observed in the 17 patients ($r = -0.7$, $p = 0.02$; Fig 1A). The GINF correlated inversely with the mean postoperative FBG concentration ($r = -0.8$, $p = 0.01$; Fig 1B), and both relationships were independent of age and sex.

Interestingly, an individual's level of whole-body insulin sensitivity did not correlate with the preoperative FBG concentration ($r = 0.3$, $p = 0.4$). The preoperative FBG level did not correlate with the peak intraoperative FBG ($r = 0.4$, p = 0.4), nor was it associated with the mean postoperative FBG concentration ($r = 0.5$, $p = 0.3$).

Multivariate regression analysis (corrected for age and sex) demonstrated a significant association between GINF and the following surrogate measures of insulin resistance: fasting plasma insulin ($p = 0.03$), HOMA-IR ($p = 0.002$), and QUICKI index ($p = 0.001$, Table 3). There was no relationship between GINF and the TG/HDL ratio ($p = 0.06$). More important, the QUICKI result also demonstrated a close inverse correlation with the peak intraoperative plasma glucose ($r = -0.593$, $p = 0.014$) and mean postoperative FBG concentration ($r = -0.542$, $p = 0.02$). There was no association between the remaining surrogate measures of insulin resistance and the peak intraoperative plasma glucose level (fasting insulin, $p = 0.09$; TG/HDL ratio, $p = 0.17$; HOMA-IR, $p = 0.051$) or mean postoperative FBG concentration (fasting insulin, $p = 0.07$; TG/HDL ratio, $p = 0.2$; HOMA-IR, $p = 0.06$; Table 3).

Comment

Our results suggest nondiabetic cardiac surgical patients have high levels of preoperative insulin resistance. It is

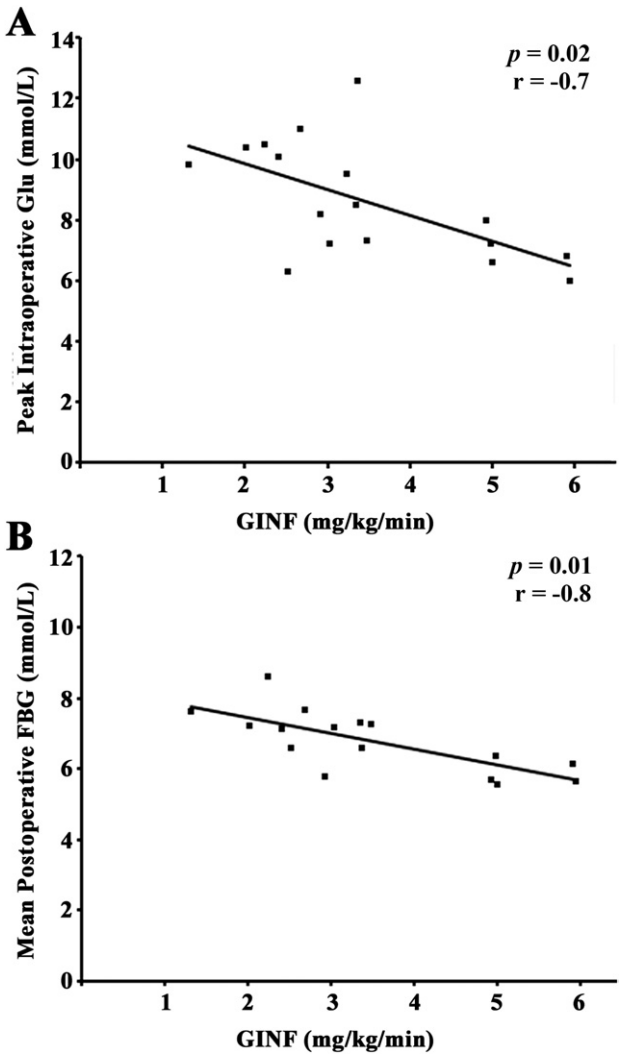

Fig 1. Representative scatter plot graphs of the (A) peak intraoperative plasma glucose concentration (mmol/L) and (B) mean postoperative plasma glucose vs mean glucose infusion rate (GINF; mg/kg/min), an index of whole body insulin sensitivity. Both graphs are corrected for age and sex. (FBG = fasting blood glucose; Glu = glucose.)

Table 3. Correlations Between Surrogate Measures of Insulin Resistance, Whole Body Insulin Sensitivity, and Perioperative Dysglycemia

		FBG	
Variable	GINF *r* Value	Intraop *r* Value	Postop *r* Value
Fasting insulin	−0.50[a]	0.58	0.46
TG/HDL ratio	−0.47	0.35	0.34
HOMA-IR	−0.69[b]	0.48	0.48
QUICKI	0.74[b]	0.58[a]	0.57[a]

Data corrected for age and sex. Multivariate linear regression. [a]$p < 0.05$; [b]$p < 0.01$.

FBG = fasting blood glucose; GINF = glucose infusion rate; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; Intraop = intraoperative; Postop = postoperative; QUICKI = Quantitative Insulin Sensitivity Check Index; TG = triglyceride.

noteworthy that the mean GINF of 3.5 ± 1.4 mg/kg/min demonstrated in this population is substantially lower compared with historical clamp studies conducted in nonobese, normoglycemic individuals. Even the most insulin-sensitive patient of this cohort was still relatively insulin resistant compared with healthy individuals [11, 17]. Our finding that cardiac surgical patients appear highly insulin resistant is not surprising considering this is a population with known cardiovascular disease and multiple metabolic risk factors, including hypertension, hypercholesterolemia, and obesity (Table 2). Nevertheless, the lack of a control group means additional studies using the clamp technique to evaluate nonsurgical patients or other surgical patients are required to confirm whether levels of insulin resistance are actually universally higher amongst all cardiac surgical patients.

A large body of evidence has accumulated showing only a minority of patients referred for elective cardiac operations are intensively assessed or treated for their metabolic risk factors [6, 18, 19]. Similar to other reports [12], our results indicate that the FBG study is a poor indicator of glycometabolic dysfunction. The preoperative FBG concentrations in this cohort were within normal reference ranges, despite having high levels of insulin resistance. The intriguing finding that the degree of insulin resistance—not FBG—predicts the degree of perioperative dysglycemia in cardiac surgical patients highlights the failure to identify serious underlying metabolic derangement that only becomes apparent during the stress state of a cardiac operation. Detection of glycometabolic dysfunction is vital, because prediabetic individuals share the same increased risk for early death after cardiac operations as diabetic individuals [6]. Gandhi and colleagues [7] showed that each 20-mg/dL increase in intraoperative FBG above 100 mg/dL is associated with a 34% increased likelihood of postoperative adverse events.

A major challenge is to identify insulin-resistant individuals in a feasible and robust manner preoperatively. Accurate clinical assessment of insulin resistance is difficult. A number of surrogate measures of insulin sensitivity have been used previously, primarily in large population studies [15, 20, 21]. These include fasting plasma insulin [14] and lipid subfractions [16]. Surrogate measures derived from dynamic tests, such as the oral glucose tolerance test, also correlate well with glucose clamp estimates of insulin sensitivity [22–24] and provide additional information about insulin secretion. The increased cost and time associated with dynamic testing means fasting surrogate measures are perhaps more feasible to include in standard surgical practice.

Of the range of surrogate measures of insulin resistance analyzed in this study, the QUICKI score, HOMA-IR, and fasting insulin concentration all correlated significantly with whole-body insulin resistance (Table 3). This in keeping with previous studies that have showed the QUICKI score and HOMA-IR are accurate indexes of insulin sensitivity over a wide range of insulin-resistant states [20, 21, 25]. An important observation is that the QUICKI score not only correlated closely with the gold standard clamp assessment of insulin resistance but was also a significant predictor of perioperative dysglycemia. This finding has potentially important clinical implications for future preoperative assessment protocols in cardiac surgical patients. As a validated surrogate index for insulin resistance, the QUICKI score may be an accurate, cost-effective method to evaluate all cardiac surgical patients for preoperative levels of insulin resistance.

Our observations raise the important question of how the implementation of metabolic screening in cardiac surgical patients would translate to improved clinical outcomes. Postoperative glucose control is a controversial topic [26]; however, multiple studies in cardiac surgical patients suggest tight glucose control using perioperative glucose, insulin, and potassium infusions leads to significant reductions in postoperative morbidity and death [6, 8, 18]. Sato and colleagues [10] used the clamp technique to measure intraoperative insulin resistance and demonstrated less intraoperative insulin resistance led to fewer complications, irrespective of preoperative diabetic status. All the same, validated assessments of the potential risks and benefits of intraoperative glycemic control are lacking, as is a universal consensus on treatment algorithms for perioperative insulin infusions.

The size of this study did not permit investigation of whether a threshold level of insulin resistance exists that predicts adverse outcomes. We are undertaking further studies to ascertain what implications the association between insulin resistance and perioperative dysglycemia may have for clinical outcomes after cardiac operations. The initiation of targeted preoperative and perioperative metabolic therapy would only be indicated if it could be demonstrated that preoperative insulin resistance is a modifiable risk factor for adverse postoperative events.

A number of limitations exist in this study. The small sample size implies caution when interpreting the absence and presence of significant correlations calculated in this study; however, the use of the reference method

clamp technique enhances the validity of our findings. The lack of a control population makes it difficult to interpret the relative severity of insulin resistance measured in this population of cardiac surgical patients compared with other surgical populations or healthy individuals. The heterogeneity of the study population and variation in disease etiology may have also influenced our results. Most of the patients were receiving statin therapy for dyslipidemia, which possibly influenced surrogate measures of insulin resistance, such as lipid ratios. We determined it was not ethical to stop these medications.

In summary, cardiac surgical patients display high levels of insulin resistance. It is the degree of insulin resistance—not the baseline FBG—that is significantly associated with the development of perioperative dysglycemia. Calculation of the QUICKI score, a surrogate marker of insulin resistance, appears a useful strategy to accurately identify insulin resistance and predict the degree of perioperative dysglycemia in cardiac surgical patients. Further studies are necessary to establish the implications of this association for postoperative outcomes.

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