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Role of Intraoperative and Postoperative Blood Glucose Concentrations in Predicting Outcomes after Cardiac Surgery

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ABSTRACT

Background: Severe hyperglycemia is associated with adverse outcomes after cardiac surgery. Whether intraoperative and postoperative glucose concentrations equally impact outcomes is unknown. The objective of this investigation was to compare the ability of perioperative glucose concentrations and glycemic variability to predict adverse outcomes. Risk associated with decreasing increments of glucose concentrations, hypoglycemia, and diabetic status was also examined.

Methods: This retrospective analysis of prospectively collected data included 4,302 patients who underwent cardiac surgery between October 3, 2005 and May 31, 2007 at the Cleveland Clinic. Time-weighted mean intraoperative (Glc_{OR}) and postoperative (Glc_{ICU}) glucose concentrations were calculated. Patients were categorized as follows: Glc more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl. Coefficient of variation was used to calculate glycemic variability. Logistic regression model with backward selection assessed the relationship between glucose concentrations, variability, and adverse outcomes while adjusting for potential confounders. Another model assessed the predictability of Glc_{OR} and Glc_{ICU} on adverse outcomes.

Results: Both Glc_{OR} and Glc_{ICU} predicted risk for mortality and morbidity. Increased postoperative glycemic variability was associated with increased risk for adverse outcomes. Severe hyperglycemia (Glc_{OR} and Glc_{ICU} > 200 mg/dl) was associated with worse outcomes; however, decreasing increments of Glc_{OR} did not consistently reduce risk. Glc_{OR} less than or equal to 140 mg/dl was not associated with improved outcomes compared with severe hyperglycemia, despite infrequent hypoglycemia. Diabetic status did not influence the effects of hyperglycemia.

Conclusion: Perioperative glucose concentrations and glycemic variability are important in predicting outcomes after cardiac surgery. Incremental decreases of intraoperative glucose concentrations did not consistently reduce risk. Despite rare hypoglycemia, intraoperative glucose concentrations closest to normoglycemia were associated with worse outcomes.

What We Already Know about This Topic

- Although hyperglycemia is associated with increased postoperative morbidity and mortality, it is unclear whether intraoperative and/or postoperative hyperglycemia are important to this association

What This Article Tells Us That Is New

- In more than 4,000 patients who underwent cardiac surgery, both intraoperative and postoperative hyperglycemia more than 200 mg/dl were associated with increased morbidity and mortality in both patients with and without diabetes
- In contrast to the postoperative setting, maintaining serum glucose close to normoglycemia (≤ 140 mg/dl) intraoperatively increased morbidity and mortality to the level of severe hyperglycemia (> 200 mg/dl)

SEVERE hyperglycemia is clearly associated with worse outcomes in hospitalized patients.[1,2] Hyperglycemia occurs commonly during the perioperative period and is associated with increased risk for mortality and morbidity.[3–5] Most investigations in surgical patients have focused on the influence of postoperative glucose concentrations on postoperative outcomes.[1,3] Fewer reports have examined the influence of glucose concentrations measured during the intraoperative period.[4,5] Moreover, none of these reports has

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examined the ability of intraoperative blood glucose concentrations to predict outcomes compared with glucose concentrations measured during the postoperative period. Thus, the importance of intraoperative *versus* postoperative glucose concentrations on adverse outcomes is unknown. Understanding the relative contribution that intraoperative *versus* postoperative glucose concentrations have on outcomes has significant implications for perioperative care of the surgical patient.

Recommendations regarding glucose control have been learned largely from investigations in intensive care units (ICUs)[1,6,7] and applied to the operating room setting. However, profound differences in effective blood glucose concentrations occur during the intraoperative period compared with glucose concentrations seen in the ICU, especially during cardiac surgery.[8–10] Thus, the ability to generalize ICU recommendations for glucose control to the operating room is uncertain and requires further investigation. For example, although incremental decreases in glucose concentrations have been associated with a decreased risk in critically ill patients,[11] whether incremental decreases in mean intraoperative blood glucose concentrations similarly moderate risk remain unknown. Furthermore, increased glucose variability has been associated with worse outcomes in critically ill patients.[11–13] However, the influence of intraoperative *versus* postoperative glycemic variability is unknown. Evaluation of risk related to incremental decreases in intraoperative blood glucose concentrations and glycemic variability will improve our understanding of glucose homeostasis during the perioperative period and may ultimately lead to improved outcomes of patients undergoing cardiac surgery.

Diabetes mellitus is common in patients undergoing cardiac surgery. Limited information is available regarding whether diabetes influences the adverse effect of hyperglycemia on morbidity and mortality. Several reports found that diabetes mellitus modified the influence of glucose levels on outcomes in critically ill patients.[14–16] Others suggested that critically ill patients with diabetes are not benefited by glucose control compared with patients without diabetes.[17] However, whether diabetes alters the influence of intraoperative glucose concentrations on outcomes is unknown and must be determined to appropriately manage the patient with diabetes during cardiac surgery.

Our primary objective was to compare the influence of intraoperative *versus* postoperative glucose concentrations on risk of postoperative adverse outcomes after cardiac surgery. Additional objectives of this study included analyzing whether glycemic variability, episodes of hypoglycemia, and diabetic status had independent effects on the mortality and morbidity of this cohort of patients undergoing cardiovascular surgery.

Materials and Methods

Perioperative patient data were obtained from the Automated Record Keeper of Department of Cardiothoracic Anesthesia at the Cleveland Clinic, which collected real-time data from the intraoperative anesthesia record electronically, and the Cardiothoracic Anesthesia Patient Registry of the Department of Cardiothoracic Anesthesia at the Cleveland Clinic. All registry data were prospectively collected, concurrent with patient care on electronic tablets, by experienced and specifically trained research personnel. Registry data that did not conform within a range of expected results were rejected and reevaluated. Research use of the Registry was approved by the Institutional Review Board (Cleveland Clinic, Cleveland, OH) and used methods that have been reported previously.[18] Individual patient consent was waived because no interventions were performed.

The study population included 4,302 patients who underwent cardiac surgery, including coronary artery bypass grafting and/or valve replacement procedures, between Oc-

Table 1. Comparison of Patients with Intraoperative Time-weighted Mean Glucose Concentration (Glc_{OR}) > 200, 171–200, 141–170, and ≤ 140 mg/dl on Continuous Baseline and Perioperative Risk Factors

Continuous Variables	Glc_{OR} > 200 mg/dl (N = 700)	Glc_{OR} = 171–200 mg/dl (N = 1,283)	Glc_{OR} = 141–170 mg/dl (N = 1,780)	Glc_{OR} ≤ 140 mg/dl (N = 539)	*P* Value
Mean glucose concentration, mg/dl	226 ± 22.4	184 ± 8	156 ± 8	130 ± 9	< 0.001
Glucose variability (CV × 100)	3.70 (3.07–4.11)	4.14 (3.69–4.52)	4.32 (3.89–4.72)	4.39 (3.83–4.85)	< 0.001
Age, yr	65 (58–74)	66 (55–74)	64 (54–73)	62 (50–72)	< 0.001
Body mass index, kg/m^2	28 (25–32)	27 (24–31)	27 (24–32)	28 (25–31)	0.113
Preoperative laboratory values					
Hematocrit, %	40 (36–43)	41 (38–44)	42 (38–45)	42 (38–44)	< 0.001
Creatinine, mg/dl	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	0.0725
Perioperative variables					
Aortic cross-clamp time, min	84 (65–109)	76 (59–97)	68 (52–87)	56 (42–76)	< 0.001

Results are shown as mean ± SD or median (25th–75th percentile). *P* value refers to the comparison among discrete ranges of mean glucose.

CV = coefficient of variation; Glc = time-weighted mean glucose concentration; OR = intraoperative.

Table 2. Comparison of Patients with Time-weighted Mean Glucose Concentrations (Glc_{OR}) > 200, 171–200, 141–170, and ≤ 140 mg/dl on Categorical Baseline and Perioperative Risk Factors

Categorical Variables	Glc_{OR} > 200 mg/dl (N = 700)	Glc_{OR} = 171–200 mg/dl (N = 1283)	Glc_{OR} = 141–170 mg/dl (N = 1780)	Glc_{OR} ≤ 140 mg/dl (N = 539)	*P* Value
Demographics					
Male gender	401 (57.3)	842 (65.6)	1250 (70.2)	388 (72)	< 0.001
Clinical history					
Hypertension	526 (75.1)	871 (67.9)	1175 (66.0)	343 (63.6)	< 0.001
Atrial fibrillation or flutter	145 (20.7)	311 (24.2)	407 (22.9)	141 (26.2)	0.117
Heart failure	213 (30.4)	347 (27.0)	430 (24.2)	148 (27.5)	0.0116
Myocardial infarction	192 (27.4)	323 (25.2)	359 (20.2)	86 (16.0)	< 0.001
Left ventricular dysfunction					< 0.001
Normal (EF > 60%)	262 (37.4)	530 (41.3)	791 (44.4)	225 (41.7)	
Mild dysfunction (EF 50–59%)	258 (36.9)	450 (35.1)	654 (36.7)	218 (40.4)	
Moderate dysfunction (EF 41–45%)	30 (4.3)	62 (4.8)	87 (4.9)	24 (4.5)	
Moderate–severe dysfunction (EF 35–40%)	35 (5.0)	61 (4.8)	81 (4.6)	23 (4.3)	
Severe dysfunction (EF < 35%)	115 (16.4)	180 (14.0)	167 (9.4)	49 (9.1)	
Pulmonary hypertension	125 (17.9)	239 (18.6)	298 (16.7)	109 (20.2)	0.255
Moderate or severe mitral insufficiency	220 (31.4)	397 (30.9)	550 (30.9)	156 (28.9)	0.797
Chronic obstructive pulmonary disease	86 (12.3)	149 (11.6)	168 (9.4)	56 (10.4)	0.112
Carotid artery stenosis (previous carotid surgery or stenosis > 40%)	130 (18.6)	188 (14.7)	227 (12.8)	60 (11.1)	< 0.001
Diabetes mellitus	315 (45.0)	311 (24.2)	317 (17.8)	81 (15.0)	< 0.001
Peripheral vascular disease	82 (11.7)	139 (10.8)	179 (10.1)	49 (9.1)	0.43
Stroke	66 (9.4)	96 (7.48)	120 (6.74)	40 (7.4)	0.155
Renal failure on peritoneal or hemodialysis	13 (1.9)	22 (1.7)	30 (1.7)	23 (4.3)	0.0016
Cardiovascular surgical history					
Previous cardiac surgery	138 (19.7)	294 (22.9)	374 (21.0)	155 (28.8)	< 0.001
Carotid surgery	46 (6.6)	63 (4.9)	60 (3.4)	16 (3.0)	0.0011
Major noncarotid vascular surgery	33 (4.7)	68 (5.3)	83 (4.7)	27 (5.0)	0.869
Cardiovascular procedure					
Coronary artery bypass grafting	442 (63.1)	663 (51.7)	795 (44.7)	168 (31.2)	< 0.001
Left internal mammary artery	299 (42.7)	437 (34.1)	552 (31)	111 (20.6)	< 0.001
Right internal mammary artery	47 (6.7)	71 (5.5)	127 (7.1)	28 (5.2)	0.199
Radial artery graft	25 (3.6)	35 (2.7)	31 (1.7)	7 (1.3)	0.0086
Saphenous vein graft	408 (58.3)	586 (45.7)	697 (39.2)	139 (25.8)	< 0.001
Aortic valve repair or replacement	242 (34.6)	298 (38.8)	596 (33.5)	188 (34.9)	0.0216
Mitral valve replacement	103 (14.7)	175 (13.6)	188 (10.6)	61 (11.3)	0.0097
Mitral valve repair	161 (23.0)	309 (24.1)	459 (25.8)	124 (23.0)	0.36
Tricuspid valve repair/replace	56 (8.0)	115 (8.96)	130 (7.3)	62 (11.5)	0.0173
Aortic surgery	54 (7.7)	106 (8.3)	125 (7.0)	55 (10.2)	0.108
Myomectomy	45 (6.4)	66 (5.1)	110 (6.2)	30 (5.6)	0.568
Maze procedure	43 (6.1)	81 (6.31)	123 (6.91)	42 (7.79)	0.615
Perioperative variables					
Emergency procedure	11 (1.6)	10 (0.8)	10 (0.6)	3 (0.6)	0.0716
Hypoglycemia					< 0.001
No hypoglycemia	610 (87.1)	1182 (92.1)	1642 (92.3)	476 (88.3)	
Mild hypoglycemia	54 (7.7)	54 (4.2)	82 (4.6)	32 (5.9)	
Moderate–severe hypoglycemia	36 (5.1)	47 (3.7)	56 (3.2)	31 (5.8)	
Patients who received intraoperative red blood cell transfusion	248 (35.4)	333 (26.0)	345 (19.4)	122 (22.6)	< 0.001

All data are expressed as N (%). *P* value refers to the comparison among discrete ranges of mean glucose.
EF = ejection fraction; Glc = time-weighted mean glucose concentration; OR = intraoperative.

tober 3, 2005 and May 31, 2007. Patients who had off-pump cardiac surgery, deep hypothermic circulatory arrest, heart transplant, or elective ventricular assist device placement were excluded from this analysis. For patients with multiple surgeries during this time period, only the first surgery and hospitalization were included in this analysis. Variables selected for this analysis are listed in tables 1 and 2.

Postoperative in-hospital adverse outcome variables as described by Higgins *et al.*[18] included (1) mortality (all-cause in-hospital mortality); (2) cardiac morbidity (combination of postoperative myocardial infarction and/or low cardiac output with a requirement for intraaortic balloon pump, ventricular assist device, or extracorporeal membrane oxygenation; where postoperative myocardial infarction is de-

fined by specific electrocardiographic findings consistent with myocardial infarction[19] with a creatine phosphokinase myocardial band of more than or equal to 50 U or aspartate aminotransferase level of more than or equal to 80 U/l, and low cardiac output is defined as a cardiac index less than 1.8 $l \cdot min^{-1} \cdot m^{-2}$ despite adequate fluid replacement and high-dose inotropes for more than 4 h); (3) neurologic morbidity defined as new postoperative focal (aphasia, decrease in limb function, or hemiparesis confirmed by clinical findings and/or computed tomographic scan) or global neurologic deficit (diffuse encephalopathy with $>$ 24 h of severely altered mental status and/or failure to awaken postoperatively); (4) prolonged intubation (duration of intubation $>$ 72 h); (5) renal morbidity defined as postoperative anuria or oliguria (urine output $<$ 400 ml/24 h) and/or institution of renal dialysis or ultrafiltration; (6) infection morbidity (culture-proven pneumonia, mediastinitis, wound infection, or septicemia with appropriate clinical findings); and (7) overall morbidity (incidence of one or more of the above morbidities, including death, because early death precludes observation of morbidity).

Glucose Measurements

Perioperative glucose values were collected, analyzed, and reported from the arterial blood gas analysis. Perioperative glucose measurements were calculated as time-weighted mean glucose within patient. Time-weighted mean glucose concentration (Glc) was calculated using the glucose values from the intraoperative course (Glc_{OR}) and the first 24 h after surgery beginning with admission to the ICU (Glc_{ICU}). All patients with a minimum of four intraoperative glucose measurements were included in the analysis to ensure that the time-weighted mean glucose concentration sufficiently described the course of intraoperative glucose measurements. Glucose measurements were collected every 49 $\pm$ 10 min (mean $\pm$ SD) and every 203 $\pm$ 29 min during the intraoperative and postoperative period, respectively. An average number of glucose values collected during the intraoperative and postoperative course was 7.0 $\pm$ 2.3 and 10.1 $\pm$ 2.3, respectively.

Glucose variability was calculated for all patients using coefficient of variation. Coefficient of variation was defined as the ratio of SD to mean glucose level. Coefficient of variation is reported as coefficient of variation $\times$ 100 (for ease of interpretability because coefficient of variation is measured in hundredths). Coefficient of variation $\times$ 100 was calculated for intraoperative (coefficient of $variation_{OR}$) and postoperative (coefficient of $variation_{ICU}$) glucose values.

Insulin treatment followed the Cleveland Clinic intraoperative and postoperative insulin infusion protocol, which used an insulin infusion adjusted for absolute blood glucose and the relative change in blood glucose measurements. The protocol called for the initiation of an insulin infusion for glucose more than 120 mg/dl before cardiopulmonary bypass or more than 150 mg/dl on cardiopulmonary bypass. The intraoperative target blood glucose level was 70–150 mg/dl. Postoperatively, the target blood glucose level was 80–150 mg/dl on the day of surgery and 80–120 mg/dl during the remainder of the postoperative stay in the ICU. The insulin therapy protocols for the intraoperative and postoperative period are described in Supplemental Digital Content 1, which includes tables demonstrating the Cleveland Clinic protocols for titration of insulin, http://links.lww.com/ALN/A575. Use of an insulin infusion during the intraoperative period, the postoperative period after admission to ICU on the day of surgery and on the postoperative day 1 was recorded. The occurrence of hypoglycemic episodes during the intraoperative and postoperative course was collected. Hypoglycemia was categorized as mild (glucose level 60–69 mg/dl), moderate (40–59 mg/dl), or severe ($\leq$ 39 mg/dl).

Statistical Analysis

Univariable comparisons for baseline characteristics and perioperative variables were made with chi-square, Fisher's exact, and Wilcoxon rank sum tests as appropriate. The time-weighted mean glucose values were calculated as the area under the curve divided by the total measurement time (time from first to last measurement) for a patient. The time-weighted mean glucose measurements Glc_{OR} and Glc_{ICU} were calculated from glucose values from the intraoperative course and first 24 h in ICU, respectively.

To evaluate the association between severe hyperglycemia (mean glucose concentration $>$ 200 mg/dl) and adverse outcomes, the outcomes were compared with univariable analysis using chi-square test between patients with Glc_{OR} more than 200 or less than or equal to 200 mg/dl and Glc_{ICU} more than 200 or less than or equal to 200 mg/dl. To further examine the association of adverse outcomes as a function of decreasing mean glucose concentration, univariable analysis compared the outcomes between patients with Glc_{OR} more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl. Glc_{ICU} was similarly compared by categorizing patients by time-weighted mean glucose concentrations into four groups of glucose levels.

Multivariable analysis was then performed using logistic regression to compare the outcomes between patients with Glc_{OR} more than 200 mg/dl or less than or equal to 200 mg/dl and Glc_{ICU} more than 200 mg/dl or less than or equal to 200 mg/dl. Variables in tables 1 and 2 that had a P value less than 0.2 when assessing their association with the outcomes on univariable analysis were initially put into the multivariable model. Backward variable selection procedure with the variables of interest (mean glucose concentrations [Glc_{OR} and Glc_{ICU}], glucose variability [coefficient of $variation_{OR}$ and coefficient of $variation_{ICU}$], and hypoglycemia) kept in was then used in the final model of assessing the association between the group and the outcomes. The same procedure was also used to compare the outcomes in patients with Glc_{OR} more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl. Glc_{ICU} was compared by similarly categorizing patients into groups of mean glucose concentrations.

Table 3. Univariable Comparison of Risk for Time-weighted Mean Glucose Concentrations (Glc) > 200 *versus* ≤ 200 mg/dl Measured during Intraoperative Period (Glc_{OR}) and First 24 Postoperative Hours in ICU (Glc_{ICU})

	Intraoperative Time-weighted Mean Glucose			Postoperative Time-weighted Mean Glucose		
Outcome	Glc_{OR} > 200 mg/dl (N = 700)	Glc_{OR} ≤ 200 mg/dl (N = 3,602)	*P* Value	Glc_{ICU} > 200 mg/dl (N = 28)	Glc_{ICU} ≤ 200 mg/dl (N = 4,274)	*P* Value
Mortality	21 (3.0)	51 (1.4)	0.003	5 (17.9)	67 (1.57)	< 0.001
Cardiac morbidity	10 (1.4)	34 (0.9)	0.24	0 (0)	44 (1.0)	0.59
Prolonged intubation	78 (11.1)	212 (5.9)	< 0.001	7 (25.0)	283 (6.6)	< 0.001
Renal morbidity	24 (3.4)	58 (1.6)	0.001	3 (10.7)	79 (1.9)	< 0.001
Serious infection	36 (5.1)	77 (2.1)	< 0.001	2 (7.1)	111 (2.6)	0.13
Neurologic morbidity	12 (1.7)	45 (1.3)	0.32	4 (14.3)	53 (1.24)	< 0.001
Overall morbidity	96 (13.7)	271 (7.52)	< 0.001	10 (35.7)	357 (8.4)	< 0.001

Values within parenthesis represent percentages.

Glc = time-weighted mean glucose concentration; ICU = intensive care unit; OR = intraoperative.

To further define the risk associated with intraoperative mean glucose (Glc_{OR}) less than or equal to 140, this group of patients was divided into groups with mean glucose level of 70–120 (N = 59) *versus* 121–140 mg/dl (N = 480). Outcomes were compared between these two glucose levels with univariable and multivariable analysis.

Patients were categorized by the presence or absence of diabetes to assess risk for patients with diabetes and examine in the multivariable logistic regression model. In addition, the presence of an interaction between diabetes and glucose concentrations on outcomes was examined to determine whether the presence of diabetes influenced the effect of glucose concentrations on outcomes.

The predictive value of Glc_{OR} and Glc_{ICU} on overall morbidity and mortality was assessed. Area under the curve (C statistics) was compared for the model of predicting overall morbidity and mortality using Glc_{OR} and Glc_{ICU} with significant covariates using receiver operating characteristic analysis.

All results were analyzed with SAS version 9.2 software (SAS Institute Inc., Cary, NC). The C statistics for overall morbidity and mortality ranged from 0.836 (Glc_{OR} overall morbidity) to 0.918 (Glc_{OR} mortality). A *P* value < 0.05 was considered as overall significance level. For pairwise comparisons with six groups, the Bonferroni correction was applied, and $P < 0.008$ was considered significant.

Results

The patient population included 4,302 patients who underwent cardiac surgery between October 3, 2005, and May 31, 2007. The distribution for mean glucose concentrations, glucose variability, baseline characteristics, and operative variables for patients with Glc_{OR} more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl are found in tables 1 and 2.

Univariable analysis for patients with severe intraoperative and postoperative hyperglycemia (Glc_{OR} and Glc_{ICU}, > 200 mg/dl) had significantly increased risk of mortality and multiple morbidities compared with patients with Glc_{OR} and Glc_{ICU} less than or equal to 200 mg/dl (table 3). After adjustment for confounding factors, patients with severe intraoperative hyperglycemia (Glc_{OR} > 200 mg/dl) had a 90% increase in odds for mortality and approximately 50% increase in odds for overall morbidity. Patients with severe postoperative hyperglycemia (Glc_{ICU} > 200 mg/dl) had a 10-fold increase in odds for mortality and greater than 3-fold increase in odds for overall morbidity (table 4).

The univariable analysis of outcomes related to mean intraoperative glucose concentrations (Glc_{OR}) more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl are depicted graphically in figure 1. Risk for adverse outcome was increased with severe hyperglycemia (Glc_{OR} > 200 mg/dl). However, risk for adverse outcome did not decrease consistently with decreasing glucose level during the intraoperative period. The risk for mortality and overall morbidity were significantly lower with mild hyperglycemia (Glc_{OR} 141–170 mg/dl) compared with severe hyperglycemia (Glc_{OR} > 200 mg/dl). However, risk for mortality and overall morbidity were similar between severe hyperglycemia (Glc_{OR} > 200 mg/dl) and glucose concentrations closest to normoglycemia (Glc_{OR} ≤ 140 mg/dl). When the analysis was adjusted for confounding variables, the results were similar (Supplemental Digital Content 2, which includes Forest plots illustrating the adjusted pairwise comparison of mean glucose concentrations on overall morbidity and mortality, http://links.lww.com/ALN/A576). Adjusted risk for mortality was 3-fold higher in patients with severe hyperglycemia (Glc_{OR} > 200 mg/dl) compared with patients with mild hyperglycemia (Glc_{OR} 141–170 mg/dl). However, odds for mortality were not significantly different between patients with severe hyperglycemia (Glc_{OR} > 200 mg/dl) and patients with glucose levels closest to normoglycemia (Glc_{OR} ≤ 140 mg/dl). To further examine the risk in the patients with glucose level less

Table 4. Comparison of Adjusted Risk for Time-weighted Mean Glucose Concentrations (Glc) > 200 *versus* ≤ 200 mg/dl and Glucose Variability (coefficient of variation) Measured during Intraoperative Period (Glc_{OR}, coefficient of $variation_{OR}$) and the First 24 Postoperative Hours in ICU (Glc_{ICU}, coefficient of $variation_{ICU}$)

Outcome	Glc_{OR}, Odds Ratio (95% CI)	Coefficient of $Variation_{OR}$, Odds Ratio (95% CI)	Glc_{ICU}, Odds Ratio (95% CI)	Coefficient of $Variation_{ICU}$, Odds Ratio (95% CI)
Mortality	1.92 (1.01–3.70)*	1.15 (0.78–1.69)	10.0 (2.86–33.3)†	1.49 (1.05–2.11)*
Cardiac morbidity	1.05 (0.46–2.22)	1.03 (0.66–1.60)	0.17 (0.001–2.22)	1.23 (0.81–1.84)
Prolonged intubation	1.64 (1.18–2.33)*	1.17 (0.96–1.41)	2.08 (0.68–6.25)	1.08 (0.90–1.31)
Renal morbidity	1.45 (0.81–2.63)	0.84 (0.59–1.18)	2.04 (0.38–11.11)	1.45 (1.05–1.99)*
Serious infection	1.85 (1.14–2.94)*	1.01 (0.76–1.35)	0.94 (0.15–5.88)	1.62 (1.23–2.13)†
Neurologic morbidity	1.15 (0.57–2.27)	0.91 (0.62–1.33)	10.0 (2.86–33.33)†	1.23 (0.86–1.75)
Overall morbidity	1.49 (1.09–2.05)*	1.09 (0.91–1.29)	3.57 (1.39–9.09)*	1.33 (1.13–1.58)†

Results are shown as odds ratio and 95% confidence interval (CI). Risk associated with coefficient of variation is shown per one unit increase.

* $P < 0.05$, † $P \leq 0.001$.

Glc = time-weighted mean glucose concentration; ICU = intensive care unit; OR = intraoperative.

than or equal to 140 mg/dl, patients with mean glucose level of 70–120 mg/dl were compared with patients with mean glucose level of 121–140 mg/dl. Mortality (1/59 [1.7%] *vs.* 9/480 [1.9%]; $P = 0.93$) and overall morbidity (6/59 [10.2%] *vs.* 51/480 [10.6%]; $P = 0.92$) were similar between groups. The results of multivariable analysis between these two levels of mean glucose were also similar.

The univariable analysis of outcomes and mean postoperative glucose concentrations (Glc_{ICU}) more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl are depicted graphically in figure 2. The risk for adverse outcome was increased with severe postoperative hyperglycemia ($Glc_{ICU} > 200$ mg/dl). In contrast to the pattern seen with intraoperative glucose levels, risk for mortality and multisystem morbidities seemed to decrease as mean postoperative glucose concentrations decreased. When the analysis was adjusted for confounding variables, the results were similar (Supplemental Digital Content 2, which includes Forest plots illustrating the adjusted pairwise comparison of mean glucose concentrations on overall morbidity and mortality, http://links.lww.com/ALN/A576). Odds ratio for mortality was 18-fold higher for patients with severe postoperative hyperglycemia ($Glc_{ICU} > 200$ mg/dl) compared with patients with postoperative glucose concentrations closest to normoglycemia ($Glc_{ICU} \leq 140$ mg/dl). Risk for overall morbidity was 5-fold higher for patients with severe postoperative hyperglycemia ($Glc_{ICU} > 200$ mg/dl) compared with patients with postoperative glucose concentrations closest to normoglycemia ($Glc_{ICU} \leq 140$ mg/dl).

Glucose variability was compared using coefficient of variation and reported as coefficient of variation × 100. Overall glucose variability was higher during the intraoperative period than during the postoperative period (mean ± SD, 4.1 ± 0.7 *vs.* 3.7 ± 0.8; $P < 0.001$). Intraoperative glucose variability was similar between nonsurvivors and sur-

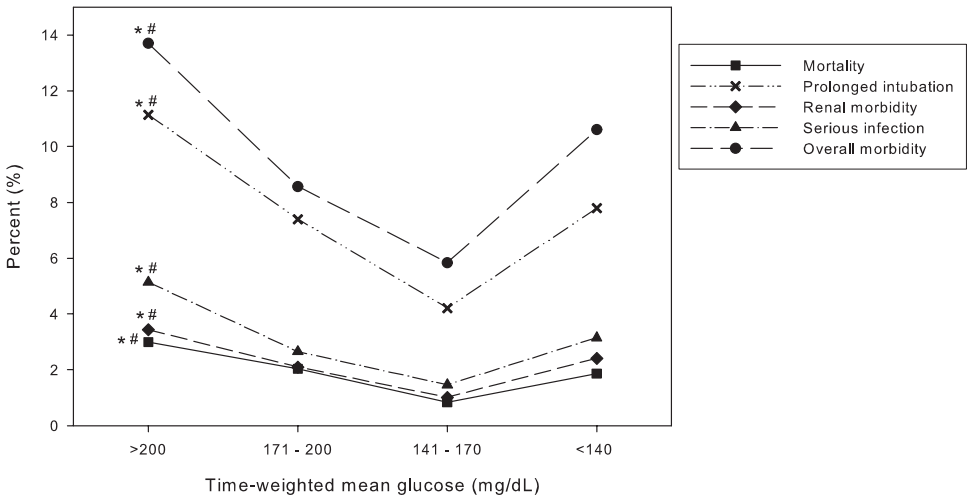

Fig. 1. Univariate analysis comparing risk of adverse outcome between decreasing incremental mean glucose levels during the intraoperative period (Glc_{OR}). * $P \leq 0.001$ overall between mean glucose levels for each individual outcome. # $P \leq 0.001$ between Glc_{OR} more than 200 mg/dl and Glc_{OR} 141–170 mg/dl. Cardiac and neurologic morbidity were not significantly different (data not shown).

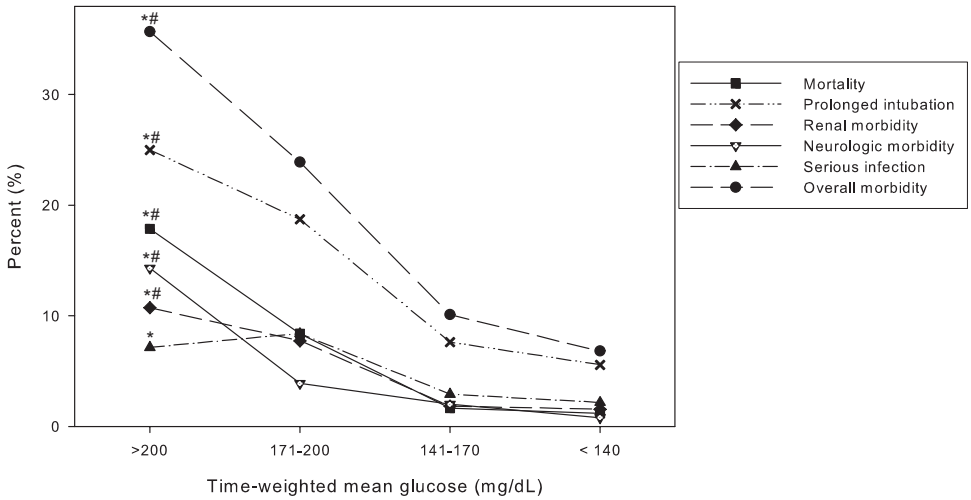

Fig. 2. Univariate analysis comparing risk of adverse outcome between decreasing incremental mean glucose levels during the initial postoperative period (Glc_{ICU}). * $P \leq 0.001$ overall between glucose levels for each individual outcome. # $P \leq 0.001$ between Glc_{ICU} more than 200 mg/dl and Glc_{ICU} 141–170 mg/dl. Cardiac morbidity was not significantly different between Glc_{ICU} more than 200 mg/dl and Glc_{ICU} 141–170 mg/dl (data not shown).

vivors (4.0 ± 0.8 *vs.* 4.1 ± 0.7; $P = 0.13$). Intraoperative glucose variability was not a significant risk factor for poor outcomes when risk was compared between patients with mean glucose level more than 200 mg/dl *versus* less than or equal to 200 mg/dl (table 4). However, postoperative glucose variability was significantly higher in nonsurvivors compared with survivors (4.3 ± 1.0 *vs.* 3.7 ± 0.8; $P < 0.001$). Increased postoperative glucose variability was associated with increased risk for mortality and overall morbidity (table 4). When mean intraoperative and postoperative mean glucose concentrations (Glc_{OR} and Glc_{ICU}) were categorized into groups of mean glucose level more than 200, 171–200, 141–170, and less than or equal to 140 mg/dl, increased postoperative, but not intraoperative, glucose variability increased the risk for adverse outcome.

Additional risk factors for the individual postoperative morbid events are listed in Supplemental Digital Content 3, which includes tables listing the factors of interest and other variables found to be significantly associated with each morbid event, http://links.lww.com/ALN/A577.

The predictability of Glc_{OR} and Glc_{ICU} was compared based on the area under the curve (C statistics) of the model. The C statistics of the model with Glc_{OR} and Glc_{ICU} for mortality was 0.918 and 0.915, respectively ($P = 0.97$). The C statistics of the model with Glc_{OR} and Glc_{ICU} for overall morbidity was 0.836 and 0.839, respectively ($P = 0.48$).

The presence of diabetes was ascertained using the Registry data. All patients with type 1, type 2, and diet-controlled diabetes were labeled as diabetic. Diabetes was present in 1,024 patients (23.8%). Unadjusted risk of mortality and morbidity of patients with diabetes and without diabetes associated with intraoperative and postoperative blood glucose concentrations are shown in figures 3 and 4. Multivariable analysis found that the presence of diabetes was an in-

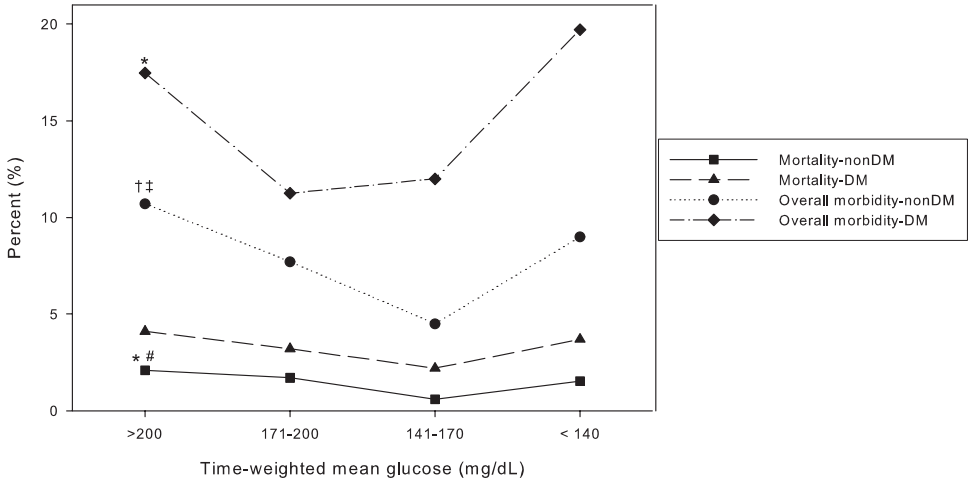

Fig. 3. Univariate analysis comparing risk of mortality and overall morbidity between patients with and without diabetes related to mean intraoperative glucose levels. * $P < 0.05$ and † $P < 0.001$ overall between levels of mean glucose within patient group. # $P \leq 0.009$ and ‡ $P < 0.001$ between Glc_{ICU} more than 200 mg/dl and Glc_{ICU} 141–170 mg/dl. DM = patient with diabetes; non-DM = patient without diabetes.

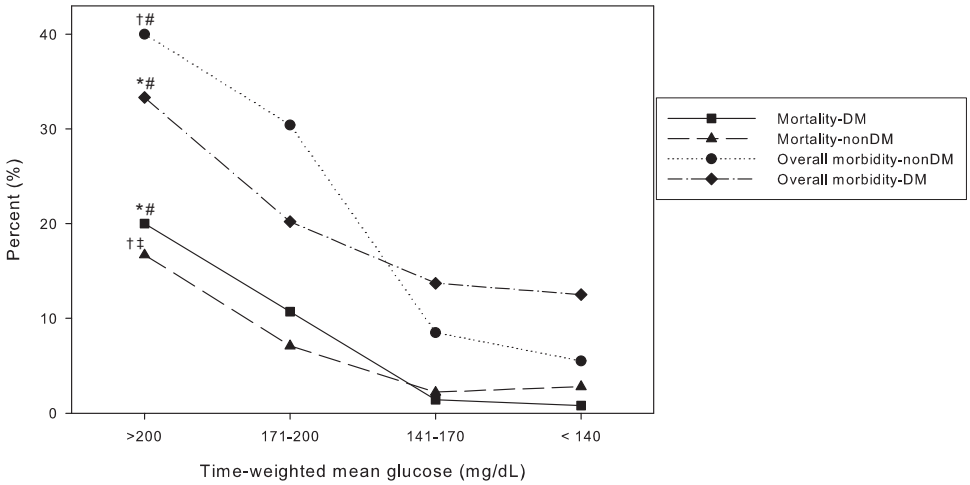

Fig. 4. Univariate analysis comparing risk of mortality and overall morbidity between patients with and without diabetes related to postoperative mean glucose levels. * $P < 0.05$ and † $P \leq 0.001$ overall between levels of mean glucose within patient group. # $P < 0.05$ and ‡ $P \leq 0.001$ between Glc_{ICU} more than 200 mg/dl and Glc_{ICU} 141–170 mg/dl. DM = patient with diabetes; non-DM = patient without diabetes.

dependent risk factor for adverse outcome. The presence of diabetes *per se* increased the risk for mortality and overall morbidity (odds ratio [95% CI] 1.97 [1.12–3.48]; $P = 0.019$ and 1.47 [1.11–1.94]; $P = 0.007$), respectively. The influence of mean glucose concentrations on outcomes was evaluated for an interaction with the presence of diabetes. No interaction was found between the influences of glucose level on outcome. The association of mean glucose concentrations with adverse outcome was not influenced by the presence of diabetes.

Perioperative insulin therapy was compared between groups. Nearly all (> 99.5%) patients received an insulin infusion intraoperatively, on admission to the ICU, and continuing through the first postoperative day.

Hypoglycemia occurred infrequently. Severe (defined as any single episode of glucose < 40 mg/dl), moderate (40–59 mg/dl), and mild (60–69 mg/dl) hypoglycemia occurred in 3 (0.07%), 16 (0.3%), and 25 (0.5%) patients, respectively, during the intraoperative period. Of these 44 (1.0%) patients, none died and seven (15.9%) experienced overall morbidity. Postoperatively, severe, moderate, and mild hypoglycemia occurred in 22 (0.5%), 130 (3.0%), and 200 (4.6%) of all patients. Of these 352 (8%) patients who developed an episode of hypoglycemia during postoperative course, 19 (5.4%) died and 56 (15.9%) experienced overall morbidity. The covariate hypoglycemia categorized patients into one of three groups: (1) no episodes of hypoglycemia; (2) an episode of mild hypoglycemia occurring during the intraoperative or postoperative course; or (3) any episode of moderate–severe hypoglycemia occurring during the intraoperative or postoperative course. Hypoglycemia, the variable of interest, was forced into the logistic regression model to determine whether it was associated with postoperative mortality or morbidity. Hypoglycemia was not significantly associated with mortality or overall morbidity ($P = 0.86$ and 0.56), respectively.

Discussion

Our investigation found that both intraoperative and postoperative glucose measurements were important predictors of outcomes after cardiac surgery. Moreover, postoperative, but not intraoperative, glycemic variability had an independent effect on morbidity and mortality. Hypoglycemia occurred infrequently and had no independent impact on outcomes. Finally, in contrast to findings among heterogeneous populations of the critically ill, patients with diabetes sustained an increased risk of mortality, but the impact of hyperglycemia was similar between patients with and without diabetes.

Patients with severe hyperglycemia (Glc > 200 mg/dl) occurring during the intraoperative or initial postoperative period were at increased risk for postoperative mortality and multisystem morbidity. However, notable differences in risk for adverse outcomes were found between the intraoperative and postoperative period when hyperglycemia was less severe. Similar to other reports,[20,21] our investigation found that decreasing mean postoperative glucose levels consistently decreased risk of mortality and multisystem morbidities. In contrast, during the intraoperative period, risk for adverse outcome did not decrease consistently as a function of mean glucose concentrations as long as the glucose concentration remained less than 200 mg/dl. Patients with mild intraoperative hyperglycemia (Glc_{OR} = 141–170 mg/dl) had lower risk of adverse outcome than did patients with severe hyperglycemia ($Glc_{OR} > 200$ mg/dl). However, risk seemed to increase as glucose levels approached closer to normoglycemia ($Glc_{OR} \leq 140$ mg/dl). Surprisingly, patients with lower glucose levels ($Glc_{OR} \leq 140$ mg/dl) were at similar risk compared with patients with severe hyperglycemia ($Glc_{OR} > 200$ mg/dl). This pattern associated with intraoperative glucose levels was evident with multiple outcomes such as mortality and several morbidities. This finding contrasts with results from an initial investigation in critically ill

patients who found significant benefit on morbidity and mortality when postoperative blood glucose was titrated to normoglycemia (80–110 mg/dl).[1] However, a recent, randomized, controlled trial in the patients who underwent cardiac surgery similarly found increased risk of adverse outcome as intraoperative glucose levels approached toward normoglycemia.[22] In addition, other reports in critically ill patients found either no benefit or increased mortality when efforts were made to achieve normoglycemia.[23–25] Our results are similar to these recent clinical trials and suggest that intraoperative mild hyperglycemia (141–170 mg/dl) is well tolerated in cardiac surgical patients and may be associated with benefits on postoperative outcomes.

Efforts were made to examine the association of adverse outcomes with glucose concentrations closest to normoglycemia; however, this analysis was limited by the fact that the majority of patients in this category ($Glc_{OR} \leq 140$ mg/dl) had mean glucose levels between 130 and 140 mg/dl, and few had mean glucose concentrations within accepted ranges for normoglycemia (70–110 mg/dl). Indeed, only four patients (0.1%) had mean intraoperative glucose levels between 70 and 100 mg/dl. However, when comparison was made between patients with mean glucose 70–120 mg/dl *versus* 121–140 mg/dl, similar risk for mortality and morbidity was found between these two glucose levels. The power of this analysis is limited by the small number of patients at the lowest glucose levels; however, the incidence of adverse outcomes seems consistent between the groups. The explanation for an increase in adverse outcome when intraoperative mean glucose levels approach closer to normoglycemia is unclear.

Our investigation found a low incidence of hypoglycemia in the operating room despite the fact that many patients in this analysis had known risk factors for hypoglycemia.[26] This may reflect the fact that arterial blood gas analysis with glucose measurements are performed frequently and routinely. In addition, the insulin protocol used in our operating room and ICU uses low-dose insulin infusions, small insulin boluses, and takes into account the rate of change of glucose levels over time, which contributes to the safety of this insulin infusion technique. The possibility that worse outcomes in patients with mean intraoperative glucose concentrations closest to normoglycemia (≤ 140 mg/dl) was related to hypoglycemia was evaluated in our analysis. Although severe hypoglycemia was rare in this investigation, the number of hypoglycemic episodes was increased by including a conservative measure for hypoglycemia (glucose level < 69 mg/dl). Our results found no association between mild or moderate–severe hypoglycemia and postoperative adverse outcomes. Consequently, the occurrence of hypoglycemia in our investigation does not seem to explain an increase in mortality and morbidity in patients with the lowest mean intraoperative glucose concentrations. Slightly more hypoglycemia was seen during the postoperative period; however, patients with the lowest mean postoperative glucose concentrations and the most hypoglycemia had improved outcomes. Our study contrasts with others that found hypoglycemia to be an independent risk factor for death.[7,12,25] However, our findings are consistent with another study of intraoperative glucose control in cardiac surgical patients that found titrating intraoperative blood glucose to normoglycemia worsened outcomes even though hypoglycemia was rare.[22] Factors other than hypoglycemia might thus contribute to poor outcomes in patients with glucose concentrations closest to normoglycemia.

Increased glucose variability measured by coefficient of variation, an accepted measure of variability, was an important predictor of adverse outcomes during the postoperative period, but not the intraoperative period. Glucose variability was increased during the intraoperative period in all patients likely related to the acute development of stress hyperglycemia, insulin resistance, and exacerbated by frequent intraoperative administration of glucose-containing cardioplegia. Similarly high levels of intraoperative glucose variability were seen in both hospital survivors and nonsurvivors. However, during the postoperative period, nonsurvivors had an increased variability compared with survivors, and an increased postoperative glucose variability was found to be a risk factor for mortality and overall morbidity. These results are consistent with other reports that found that increased glucose variability was associated with increased morbidity and mortality in critically ill patients.[11,12,27] In fact, some have suggested that measures of glucose variability may be a better predictor of adverse outcome than mean glucose concentrations.[11] Thus, it is possible that methods aimed at decreasing postoperative glucose variability may improve outcomes. Perhaps, if excessive intraoperative glucose variability could be decreased, intraoperative glycemic variability may be found to be a risk factor for postoperative morbidity and mortality as well.

Many prospective investigations of glucose control have been performed in the critical care setting, and these results have been generalized to the operating room. However, issues specific to the operating room, especially cardiac surgery, differ significantly from the ICU. These differences may contribute to our finding that similar mean glucose concentrations (≤ 140 mg/dl) were associated with worse outcomes during the intraoperative period but improved outcomes during the postoperative period. Certainly, the underlying factors affecting intraoperative glucose concentrations during cardiac surgery, including the hypermetabolic stress response, development of insulin resistance, use of cardiopulmonary bypass, hypothermia,[8] and administration of glucose-containing cardioplegic solutions,[9] differ significantly from causes of postoperative hyperglycemia. Furthermore, the intraoperative course is complicated by myocardial ischemia and reperfusion injury related to aortic cross-clamping and release, and the glucose concentrations may play a unique role during this period, because increased glucose uptake and metabolism during ischemia, rather than fatty acids, results in lower myocardial oxygen consumption, greater myocardial efficiency,[28,29] decreased arrhythmogenic substrates,[30,31] and preserved myocardial function.[32] In fact, severe myocardial dysfunction may result if glucose utiliza-

tion is not increased.[33–36] Glucose-insulin-potassium infusions have been administered during myocardial infarction[31,37] and cardiac surgery,[38] with purported benefits related to increased myocardial glucose utilization, although results of glucose-insulin-potassium trials have been inconsistent.[39–41] Whether patients with the lowest intraoperative mean glucose levels (≤ 140 mg/dl) experienced inadequate myocardial utilization of glucose, possibly contributing to increased postoperative complications, has not been investigated. Other factors that are significantly different between the operating room setting and the ICU include the duration of insulin treatment. Certainly, it has been suggested that short-term insulin therapy for less than 3 days will not provide a benefit on patient outcomes.[17,42] In summary, our findings emphasize that differences may exist regarding the impact of glucose concentrations in the operating room compared with the critical care unit and imply that the results from investigations of glucose concentrations in critically ill patients may not be generalizable to the cardiac surgical operating room setting. The optimal target for intraoperative glucose control remains unknown.

Although severe hyperglycemia has been associated with adverse patient outcomes, intervention to normalize glycemia has yielded inconsistent results. Whether hyperglycemia is a risk factor for adverse outcome or merely a marker for severity of illness cannot be determined from our observational investigation. Furthermore, it is unclear whether associated benefits on outcomes result from treatment of hyperglycemia *versus* benefits related to insulin therapy. Because insulin is the sole clinically effective therapy available, it is difficult to separate the effects of insulin from those of normalizing blood glucose in hyperglycemic patients. Certainly, insulin has many beneficial effects, including decreased platelet activation,[43,44] antiinflammatory effects, improved myocardial perfusion,[45,46] inotropic, and direct cardioprotective effects.[47] Several reports found insulin use to be associated with death and other complications,[48,49] which suggested that improved outcomes were related to glucose control rather than insulin administration. Nearly all (> 99.5%) the patients in this investigation received a perioperative insulin infusion. Because all patients received a similar therapy, it is unlikely that systemic insulin would explain differences in outcomes.

Diabetes is common in patients undergoing cardiac surgery. Because of chronic hyperglycemia and other alterations in glucose homeostasis, the benefit of glucose control may differ in patients depending on their diabetic status. Our investigation found that patients with diabetes experienced worse outcomes compared with patients without diabetes. Indeed, the presence of diabetes *per se* doubled the risk of mortality. However, no interaction was found between the presence of diabetes and the influence of hyperglycemia on outcomes. In other words, patients with diabetes, despite being at increased risk for adverse outcome because of having diabetes, were at similar risk as patients without diabetes related to the degree of hyperglycemia. Our results differ from other reports, which found that patients with diabetes differ from patients without diabetes in either the risk received from hyperglycemia or the benefits related to glucose control. For example, investigators reported that mortality increased with median glucose levels to a greater extent in critically ill patients without diabetes than patients with diabetes,[14,15] and insulin therapy did not provide similar benefits to patients with diabetes.[15,17] Others found that hyperglycemia was strongly associated with outcome in critically ill patients without diabetes, but not in patients with diabetes.[16] Further investigation is needed to examine pathophysiologic differences between patients with and without diabetes and the influence of mean glucose concentrations on outcomes.

There are limitations to this investigation. This study was a retrospective analysis and is thus subject to the limitations inherent in this type of study. This investigation may be subjected to selection bias although our analysis included all patients undergoing specific cardiac surgeries within a certain time period. Although our analysis adjusted for 38 baseline variables and perioperative characteristics, other unmeasured variables could significantly affect the association with outcomes and, therefore, confound the results. This retrospective analysis can only find an association rather than imply causation between measures of glucose control and adverse outcomes, and therefore, this investigation was not designed to test whether intensive glycemic control improves postoperative outcomes in patients who underwent cardiac surgery. The fact that the postoperative ICU glucose concentrations had a stronger correlation with the outcomes than the intraoperative period may be, in part, because postoperative glucose concentrations occur temporally closer to the outcomes. The effects of insulin therapy or glycemic control are difficult to distinguish. In addition, methods for detecting morbidities in the current study captured only the most severe complications and were insensitive to less critically severe outcomes.

In summary, both intraoperative and postoperative glucose concentrations are important indicators of postoperative morbidity and mortality. Although severe perioperative hyperglycemia is associated with an increased risk of adverse outcome, incremental decreases in mean glucose concentrations did not consistently moderate risk during the intraoperative period. Interestingly, mean intraoperative glucose concentrations closest to normoglycemia were not associated with the lowest risk for adverse outcome, and this increase in risk was not explained by the occurrence of hypoglycemia. Furthermore, increased postoperative glycemic variability was associated with increased risk for adverse outcomes. Perhaps, beneficial effects on outcomes may result from a higher target range of intraoperative glucose concentrations and lower perioperative glycemic variability, but this remains a subject for further investigation.

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