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Poor Intraoperative Blood Glucose Control Is Associated with a Worsened Hospital Outcome after Cardiac Surgery in Diabetic Patients

Alexandre Ouattara, M.D., Patrick Lecomte, M.D.,† Yannick Le Manach, M.D.,† Marc Landi, M.D.,* Sophie Jacqueminet, M.D.,‡ Igor Platonov, M.D.,† Nicolas Bonnet, M.D.,§ Bruno Riou, M.D., Ph.D.,‖ Pierre Coriat, M.D.#*

Background: **Tight perioperative control of blood glucose improves the outcome of diabetic patients undergoing cardiac surgery. Because stress response and cardiopulmonary bypass can induce profound hyperglycemia, intraoperative glycemic control may become difficult. The authors undertook a prospective cohort study to determine whether poor intraoperative glycemic control is associated with increased intrahospital morbidity.**

Methods: **Two hundred consecutive diabetic patients undergoing on-pump heart surgery were enrolled. A standard insulin protocol based on subcutaneous intermediary insulin was given the morning of the surgery. Intravenous insulin therapy was initiated intraoperatively from blood glucose concentrations of 180 mg/dl or greater and titrated according to a predefined protocol. Poor intraoperative glycemic control was defined as four consecutive blood glucose concentrations greater than 200 mg/dl without any decrease in despite insulin therapy. Postoperative blood glucose concentrations were maintained below 140 mg/dl by using aggressive insulin therapy. The main endpoints were severe cardiovascular, respiratory, infectious, neurologic, and renal in-hospital morbidity.**

Results: **Insulin therapy was required intraoperatively in 36% of patients, and poor intraoperative glycemic control was observed in 18% of patients. Poor intraoperative glycemic control was significantly more frequent in patients with severe postoperative morbidity (37% *vs.* 10%; $P < 0.001$). The adjusted odds ratio for severe postoperative morbidity among patients with a poor intraoperative glycemic control as compared with patients without was 7.2 (95% confidence interval, 2.7–19.0).**

Conclusion: **Poor intraoperative control of blood glucose concentrations in diabetic patients undergoing cardiac surgery is associated with a worsened hospital outcome after surgery.**

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* Assistant Professor, † Staff Anesthesiologist, Department of Anesthesiology, ‡ Assistant Professor, Department of Diabetology, § Assistant Professor, Department of Thoracic and Cardiovascular Surgery, ‖ Professor of Anesthesiology and Critical Care and Chairman, Department of Emergency Medicine and Surgery, # Professor of Anesthesiology and Critical Care and Chairman, Department of Anesthesiology.

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Address reprint requests to Dr. Ouattara: Département d'Anesthésie-Réanimation, Hôpital Pitié-Salpêtrière, 47 boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Address electronic mail to: alexandre.ouattara@psl.ap-hop-paris.fr.

NUMEROUS clinical studies have reported an increase in perioperative morbidity among diabetic patients undergoing cardiac surgical procedures.[1–4] Although diabetes mellitus has been identified as an independent risk factor of morbidity and even mortality after cardiac surgery in large cohort studies,[3–7] other recent studies have clearly demonstrated that perioperative glycemic control improves early clinical outcome of diabetic patients.[8–10] Various mechanisms by which hyperglycemia could affect clinical outcome have been identified. Hyperglycemia provokes numerous deleterious effects on myocardium subjected to ischemia–reperfusion process. In both diabetics and hyperglycemic dogs, the myocardial infarct size is strongly correlated with blood glucose concentration.[11] Moreover, high blood glucose concentration abolishes ischemic preconditioning[11] and amplifies reperfusion injuries.[12] Because hyperglycemia provokes coronary endothelial dysfunction,[13,14] it may further increase the incidence of myocardial ischemic events. The beneficial effects of glycemic control may be also related to the metabolic effects of insulin, including a decrease in concentration of free fatty acids[15] and the scavenging of free radicals.[16] Unfortunately, most clinical studies in which the beneficial effect of glucose control has been demonstrated were focused on the postoperative period. However, cardiopulmonary bypass (CPB) usually induces severe hyperglycemia, which may involve several mechanisms.[17–21] Consequently, intraoperative glycemic control may be rendered difficult despite insulin therapy.[18,22,23] Although previous studies have reported that strict intraoperative glycemic control during CPB improves immune function of diabetic patients,[18] few previous clinical studies have evaluated the impact of intraoperative glycemic control on the postoperative outcomes.[10] Therefore, we hypothesized that poor intraoperative glycemic control could be associated with worsened hospital outcome in diabetic patients undergoing heart surgery.

Materials and Methods

Study Population

This study was approved by our ethical committee (Comité de Protection des Personnes se. Prêtant à la Recherche Biomédicale, CCPPRB Pitié-Salpêtrière, Paris, France). Although care of patients conformed to the

standard procedure currently used at our institute, written informed consent was obtained from each patient included in this study. Between January 20, 2003, and September 30, 2003, all diabetic patients requiring active therapy based on oral hypoglycemic drugs or insulin and undergoing on-pump heart surgery were prospectively enrolled in our study. Patients in whom diabetes was controlled by diet alone were excluded from this current study. We excluded also patients undergoing off-pump coronary artery bypass graft. For each patient, preoperative risk factors of morbidity and mortality (*i.e.*, demographic characteristics, principles identified comorbidity factors, preoperative medication) and intraoperative data (type of procedure, duration of cardiopulmonary bypass, requirement for erythrocyte transfusion, intraoperative blood glucose concentrations) were prospectively entered into a database for later analysis.

Perioperative Management

All treated diabetic patients undergoing cardiac procedures at our institute received a standardized service local protocol established by endocrinologist, surgeons, cardiologists, and anesthesiologists over a 6-month period. The aim of this protocol was to standardize the titration of insulin therapy during the perioperative period. Therefore, for elective cardiac procedures, this protocol required the withdrawal of any preoperative diabetic treatment on the evening of the day before surgery, except for metformin, which was discontinued 1 week before heart surgery. The treatment was replaced with 0.15 U/kg subcutaneous intermediary insulin (Umuline NPH; Lilly, Suresnes, France) with additional subcutaneous fast-acting insulin (Actrapid HM; Novo Nordisk Pharmaceutique, Puteaux, France) according to blood glucose concentrations (BGL). In addition to the implementation of this protocol, an infusion of dextrose solution was started (5 g/h). After fasting overnight, all patients received a premedication based on 1 mg/kg midazolam and 0.1 mg/kg morphine subcutaneously the morning of the surgery. After BGL measurement, all patients systematically received a further subcutaneous injection of 0.15 U/kg intermediary insulin on the morning of surgery (Umuline NPH). All other medications were taken until the day of the surgery, except for antagonists of converting enzyme inhibitors, which were stopped the day before surgery.

During the intraoperative period, the infusion of dextrose was maintained at the same rate (*i.e.*, 5 g/h). BGL was measured immediately after the induction of anesthesia and was repeated every 30 min. An aggressive insulin therapy, based on continuous infusion of fast-acting insulin (Actrapid HM), was initiated as soon as BGL exceeded 180 mg/dl. Subsequently, its infusion rate was titrated according to a protocol (appendix) modified from the Portland protocol.[9] The objective of the current protocol was to maintain an intraoperative blood glucose concentration between 150 and 200 mg/dl as previously recommended.[9,10,18] To ensure that intravenous insulin therapy was rapidly administered to the patient, it was systematically infused through a peripheral venous catheter into which dextrose was also infused. Poor intraoperative glycemic control was defined as four consecutive blood glucose concentrations greater than 200 mg/dl without any decrease until the end of the surgical procedure despite the insulin therapy administered according to the protocol. For all patients, a total intravenous anesthesia protocol, based on midazolam or propofol and sufentanil or remifentanil, was used. No inhaled anesthetics agent was used intraoperatively. Antibiotic cover during the study followed our normal protocol and was based on cefamandole, except for patients with allergy for penicillin, in whom vancomycin associated with gentamicin was preferentially used. Antifibrinolytic treatment was based on aprotinin (1 million Kallikrein Inactivator Units after induction of anesthesia and in the priming solution followed by a continuous infusion of 250,000 Kallikrein Inactivator Units/h until the end of the surgery). The CPB used a membrane oxygenator with nonpulsatile flow. The choice of normothermia (36°–37°C), mild hypothermia (32°–36°C), and hypothermia (30°–32°C) during the CPB was left to the discretion of the surgeon. No dextrose solution was included in the priming volume. All drugs used intraoperatively were diluted in sterile water or saline solution. During the postoperative period, all patients were aggressively treated with either subcutaneous or continuous intravenous insulin therapy to maintain a BGL less than 140 mg/dl throughout the stay in the intensive care unit, as was recently recommended.[24] A continuous fast-acting insulin infusion (Actrapid HM) was used in the intensive care unit according to a standard protocol (table 1) in following circumstances: (1) when insulin therapy was the usual antidiabetic treatment of the patient, (2) if inotropic support was required for weaning from CPB, (3) if the intraoperative infusion insulin rate exceeded 2 U/h, (4) if there was an unstable hemodynamic state necessitating any drugs, (5)

Table 1. Postoperative Intravenous Insulin Protocol

Blood Glucose, mg/dl	Rate of Infusion, U/h	Additional Intravenous Bolus, U
< 80	Stop insulin, and 10-ml bolus of 30% dextrose is given. Check new BGL 30 min later.	
80–99	0.5	0
100–124	1	0
125–159	2	0
160–199	4	0
200–234	6	0
235–274	8	2
≥ 275	8	5

BGL = blood glucose concentration.

From Furnary *et al.*[8]; adapted from the Portland protocol with permission.

if an intensive care unit duration of stay greater than 24 h was expected, or (6) if the postoperative glycemic control was difficult by subcutaneous insulin therapy. In other cases, subcutaneous insulin therapy was administered according to the following protocol: An intermediary insulin (Umuline NPH) was given subcutaneously twice daily (0.15 U/kg). Additionally, BGL were adjusted every 4 h by subcutaneous fast-acting insulin (Actrapid HM): less than 110 mg/dl, 0 U; 110–144 mg/dl, 2 U; 145–179 mg/dl, 4 U; 180–219 mg/dl, 6 U; greater than 220 mg/dl, 8 U. Measurements of BGL were performed by finger stick or arterial line drop sampling by using a glucose analyzer (AccuData GTS; Boehringer Mannheim Corporation, Indianapolis, IN).

Major Outcomes

The primary outcome was severe in-hospital morbidity as recently defined in the cardiac surgical population[25,26] and including at least one of the following adverse outcomes: (1) cardiovascular outcome (low cardiac output and/or hypotension treated with an intraaortic balloon pump and/or two or more intravenous inotropes or vasopressors greater than 24 h, malignant arrhythmia [asystole, ventricular tachycardia, or fibrillation] requiring cardiopulmonary resuscitation, antiarrhythmia therapy, or defibrillator implantation); (2) respiratory outcome (mechanical ventilation for more than 48 h, reintubation, tracheostomy); (3) neurologic outcome (focal brain injury with permanent functional deficit, irreversible encephalopathy); (4) renal outcome (acute renal failure necessitating dialysis); (5) infectious outcome (septic shock with positive blood cultures, deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement); or (6) other outcome (any surgical or invasive procedure necessary to treat a postoperative adverse event associated with the initial cardiac surgery). The secondary outcomes were the in-hospital mortality and a prolonged stay in the intensive care unit (> 96 h). The postoperative data were prospectively collected in a database for further analysis. All data were reviewed by two independent investigators (A. O. and P. L). In case of disagreement between the two experts, a consensus was reached with a third expert.

Statistical Analysis

The sample size was based on the facts that, in our cardiac surgical population, the occurrence of diabetes mellitus was approximately of 20%, and the severe postoperative morbidity rate was approximately of 25%. With an α error of 0.05, a β error of 0.20 (power = 80%), and r^2 of 0.3 for other usual predictors of severe morbidity as defined, 189 patients were required to detect an odds ratio of 2.0. Anticipating a 5% loss to follow-up, this number was increased to 200 patients.

Univariate comparisons between patients with or without severe morbidity during their intensive care unit stay were performed by using a chi-square test or Fisher exact test where appropriate for dichotomous variables and by the Student *t* test or Wilcoxon rank test according to their distribution for continuous variables. All perioperative predictors identified in the univariate analysis were included in a multivariate logistic regression analysis. A backward conditional method was used for variable selection. No more than 1 variable per 10 outcome events was entered in the final logistic model to avoid overfitting. Calibration and discrimination of the logistic model were assessed using the Hosmer and Lemeshow chi-square statistic ($P > 0.05$ for no difference between predictive model and observed data) and the receiver operating characteristic curve, respectively. Colinearity between potential predictors was assessed with a bivariate analysis. To reveal possible heterogeneity in odds ratios between subgroups of patients, interactions terms were assessed. The 95% confidence interval (CI) of ratios was calculated. Perioperative blood glucose concentrations were compared by using repeated-measures analysis of variance and the Newman-Keuls test. Data are expressed as mean ± SD. Percentages are associated with their 95% CIs. All *P* values were two tailed, and a *P* value of less than 0.05 was considered significant. All analyses were performed using SPSS 11.5 (Chicago, IL).

Table 2. Characteristics of Postoperative Adverse In-hospital Outcomes (n = 57)

Two or more intravenous inotropes and/or vasopressors during > 24 h	35 (61)
Perioperative use of intraaortic balloon pump	7 (12)
Cardiac arrest with ventricular fibrillation	1 (2)
Mechanical ventilation for > 48 h or tracheostomy	18 (32)
Reintubation	4 (7)
Neurologic injury with permanent functional deficit	9 (16)
Acute renal failure requiring dialysis	7 (12)
Septic shock with positive blood culture	4 (7)
Reexploration for hemorrhage	2 (4)

Data are expressed as number (%). Because several adverse outcomes may occur in the same patient, the sum of percentages is greater than 100%.

Results

Between January and September 2003, 1,146 consecutive patients underwent cardiac surgical procedures in our heart institute. Among these patients, 207 (18%) patients were known as diabetic patients under medical treatment. Seven patients were excluded from this study (5 patients in whom an off-pump coronary artery bypass grafting procedure was finally decided by the surgeon and 2 patients in whom intraoperative blood glucose concentrations were not available). Consequently, a total of 200 patients were included in our analysis. The overall

Table 3. Baseline Characteristics of Diabetic Patients Included in the Study

Variable	No Postoperative Morbidity (n = 143)	Postoperative Morbidity (n = 57)	*P* Value
Age, yr	66 ± 9	68 ± 10	0.25
Sex, M:F	115:28	39:18	0.08
Body mass index, kg/m^2	27.4 ± 4.0	26.4 ± 4.4	0.18
LVEF, %	58 ± 12	51 ± 16	< 0.001
History of atrial fibrillation, n (%)	16 (11)	11(19)	0.27
Peripheral vascular disease, n (%)	25 (17)	14 (26)	0.35
Hypertension, n (%)	118 (83)	43 (75)	0.36
History of recent myocardial infraction, n (%)	16 (11)	7 (12)	0.96
Pulmonary hypertension,* n (%)	3 (2)	15 (26)	< 0.001
History of cerebrovascular disease, n (%)	7 (5)	6 (11)	0.10
Preoperative plasma creatinine, μm	97 ± 23	125 ± 70	< 0.001
Chronic obstructive pulmonary disease, n (%)	17 (12)	12 (21)	0.16
Emergency procedure, n (%)	8 (6)	8 (14)	0.09
EuroSCORE	3 ± 2	6 ± 3	< 0.001
Preoperative medications, n (%)			
ACEI	72 (50)	34 (60)	0.24
β Blockers used	92 (64)	23 (40)	0.003
Aspirin	83 (58)	33 (58)	0.98
Diabetic control, n (%)			
Oral agent	99 (69)	35 (60)	0.37
Insulin	44 (31)	23 (40)	0.02
Type of surgery, n (%)			
CABG	108 (76)	30 (53)	0.002
Valve	15 (10)	11 (19)	0.08
Combined procedure	20 (14)	16 (28)	0.05
Preoperative blood glucose concentration, mg/dl	142 ± 46	152 ± 62	0.16
Poor intraoperative glycemic control, n (%)	14 (10)	21 (37)	< 0.001
Cardiopulmonary bypass time, min	74 ± 24	84 ± 28	0.01
Aortic clamping time, min	57 ± 23	62 ± 24	0.13
Hypothermic CPB†	28 (20)	18 (32)	0.07
Intraoperative erythrocyte transfusion, n (%)	25 (17)	33 (58)	< 0.001

Data are presented as mean ± SD or number (%).

* Systolic pulmonary artery pressure greater than 50 mmHg. † Hypothermic cardiopulmonary bypass was defined by a hypothermic systemic perfusion of 32°C or lower.

ACEI = angiotensin-converting enzyme inhibitors; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; EuroSCORE = European Stratification of Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction.

in-hospital severe morbidity rate was 29% (95% CI, 23–35%). The distribution of different morbidities is summarized in table 2. Baseline clinical characteristics of patients with and without severe morbidity are presented in table 3. During the intraoperative period, an insulin infusion was initiated in 71 patients (36%; 95% CI, 29–42%). Among these patients, 35 (50%; 95% CI, 34–67%) had poor intraoperative glycemic control despite aggressive insulin therapy. During the period spent in intensive care unit, BGLs were comparable between patients with and without postoperative morbidity (data not shown). However, because BGLs at arrival in the intensive care unit were significantly higher in patients who exhibited poor intraoperative glycemic control (208 ± 54 *vs.* 148 ± 41 mg/dl; $P < 0.001$), BGL in this group was more difficult to normalize in the early postoperative period (data not shown). Poor intraoperative glycemic control was significantly more frequent in patients with severe intrahospital morbidity (table 3). Intraoperative BGLs were significantly higher in patients with severe postoperative morbidity (fig. 1A) and in patients in whom intraoperative glycemic control was poor (fig. 1B). As shown in figure 2, all in-hospital morbidities, except for infectious morbidity ($P = 0.09$), were significantly more frequent in patients who exhibited poor intraoperative glycemic control.

Multivariate analysis identified poor glycemic control as an independent risk factor of severe morbidity (table 4). The adjusted odds ratio for postoperative severe morbidity among diabetic patients who had poor intraoperative glycemic control as compared with patients who were well controlled was 7.2 (95% CI, 2.7–19.0). The Hosmer and Lemeshow statistic was 7.57 ($P = 0.48$), and the area under the receiver operating characteristic curve was 0.86 (95% CI, 0.81–0.92). No heterogeneity in the increase of morbidity among the patients with poor intraoperative glycemic control was found between subgroups of patients according to main risk factors in cardiac surgery (table 5). In diabetic patients who exhibited poor intraoperative glycemic control, the overall in-hospital mortality rate was significantly higher (11.4% *vs.* 2.4%; $P < 0.05$), and a prolonged intensive care unit duration of stay was more frequently observed (46% *vs.* 19%; $P < 0.001$).

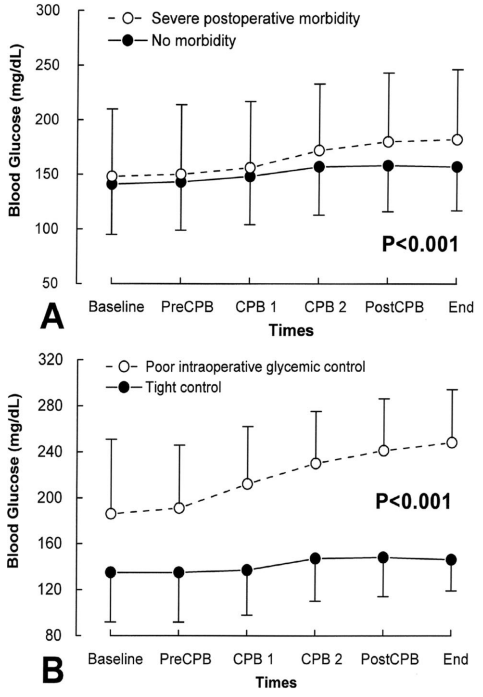

Fig. 1. Intraoperative blood glucose concentrations between diabetic patients with (n = 57) and without (n = 143) postoperative severe morbidity (*A*) and between patients in whom the intraoperative glycemic control was poor (n = 35) or tight (n = 165) (*B*). Baseline = morning of the surgery; CPB = cardiopulmonary bypass; CPB 1 = at the beginning of cardiopulmonary bypass; CPB 2 = at the end of the cardiopulmonary bypass; end = at the sternal closure; PreCPB = after induction of anesthesia but before cardiopulmonary bypass; PostCPB = after the weaning of cardiopulmonary bypass. Data are presented as mean ± SD. *P* value refers to between-group comparison.

Discussion

The main findings of this prospective observational study in diabetic patients undergoing cardiac surgery are that (1) poor intraoperative glycemic control despite aggressive insulin therapy occurred in 18% of cases, and (2) poor intraoperative glycemic control is associated with a worsened in-hospital outcome after cardiac surgery.

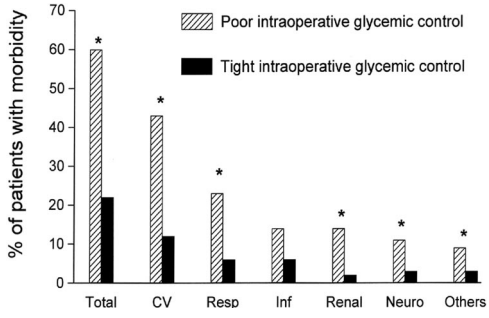

Fig. 2. Incidence of severe in-hospital morbidity between patients in whom intraoperative glycemic control was poor or tight. CV = cardiovascular morbidity; Inf = infectious morbidity; Neuro = neurologic morbidity; Resp = respiratory morbidity (see text for definitions of different morbidities). * *P* < 0.05 *versus* tight control.

Table 4. Independent Risk Factors of Severe Adverse In-hospital Outcome in Diabetic Patients after On-pump Cardiac Surgery (n = 200)

Variable	Odds Ratio (95% CI)	*P* Value
Pulmonary hypertension*	12.4 (2.7–57.4)	0.001
Poor intraoperative glycemic control	7.2 (2.7–19.0)	< 0.001
Intraoperative erythrocyte transfusion	5.4 (2.3–12.6)	< 0.001
Hypothermic CPB†	3.0 (1.2–7.3)	0.01
Preoperative plasma creatinine	1.02 (1.00–1.03)‡	0.001
Cardiopulmonary bypass time	1.02 (1.01–1.04)§	0.01

Hosmer Lemeshow statistic associated with the current model is 7.57 (P = 0.48).

* Systolic pulmonary artery pressure greater than 50 mmHg. † Hypothermic cardiopulmonary bypass was defined by a systemic temperature less than 32°C. ‡ Odds ratio per 1 μM increase. § Odds ratio per minute bypass time increase.

CI = confidence interval; CPB = cardiopulmonary bypass.

Diabetes mellitus has been identified as an independent risk factor of adverse outcome after cardiac surgery.[4–7] The prevalence of diabetes mellitus in our cardiac population was 18% and was consistent with previous studies.[2,27] Although diabetes mellitus is a well-recognized risk factor of poor outcomes after cardiac surgery,[4–7] few trials have identified the independent risk factors of poor outcome in diabetic patients undergoing heart surgery. In a large prospective cohort of diabetic patients undergoing coronary artery bypass grafting, Thourani *et al.*[4] identified age, procedure status, female sex, and hypertension as independent risk factors of mortality. In our study, by using multivariate analysis, we identified six perioperative risk factors of severe in hospital morbidity, including poor intraoperative glycemic control. Nevertheless, the strongest of these risk factors was a preoperative pulmonary hypertension, a variable that has previously been shown to be an important risk factor in the general cardiac surgical population.[27,28] We also identified the use of systemic hypothermia during CPB as an independent risk factor of severe in-hospital morbidity. The CPB-induced hyperglycemia is principally related to the release of stress hormone decrease in peripheral use of glucose and decrease in insulin secretion.[17,20,21] This latter seems to be more severely affected during hypothermic CPB.[17,21] Although we did not measure intraoperative plasma insulin concentrations, we were unable to find significant interaction between hypothermic CPB and poor intraoperative glycemic control to predict severe postoperative morbidity (table 5). Several randomized studies previously demonstrated the advantages of normothermic CPB on either postoperative early hemodynamic profile or transfusion requirement.[29,30] Nevertheless, to our knowledge, our study is the first to demonstrate an association between hypothermic systemic perfusion and worse outcome in diabetic patients. Perioperative glycemic control by aggressive insulin therapy has been reported to improve outcome in diabetic patients undergoing

Table 5. Odds Ratio for Severe Postoperative Adverse Outcome after Cardiac Surgery in Relation to the Poor Intraoperative Glycemic Control in Patient Subgroups

	With Postoperative Morbidity		Without Postoperative Morbidity				
Characteristics	n	Poor Glycemic Control, n (%)	n	Poor Glycemic Control, n (%)	Odds Ratio (95% CI)	HL Statistic	Interaction†
Age							
< 70 yr	29	10 (35)	82	5 (8)	5.6 (1.6–19.1)	0.85	NS
≥ 70 yr	28	11 (38)	61	9 (11)	10.9 (2.3–51.5)	0.33	
Sex							
Female	18	8 (44)	28	2 (7)	83.9 (5.9–1,190)	0.83	NS
Male	39	13 (33)	115	12 (10)	5.0 (1.7–14.7)	0.32	
Body mass index							
< 30 kg/m^2	43	13 (30)	109	7 (6)	5.7 (1.7–19.2)	0.24	NS
≥ 30 kg/m^2	14	8 (57)	34	7 (20)	115 (3.2–4,046)	0.76	
Preoperative insulin treatment							
Yes	22	6 (27)	29	3 (10)	4.3 (0.7–25.9)	0.63	NS
No	35	15 (43)	114	11 (10)	11.7 (3.7–36.6)	0.28	
Left ventricular ejection fraction							
< 50%	25	9 (36)	26	3 (11)	5.3 (1.05–26.6)	0.43	NS
≥ 50%	32	12 (37)	117	11 (9)	9.7 (3.0–31.0)	0.16	
Preoperative renal failure							
Yes	39	14 (36)	126	13 (10)	7.7 (2.5–23.5)	0.14	NS
No	18	7 (39)	17	1 (6)	16.1 (1.5–1.8)	0.58	
Complex surgery							
Yes	41	15 (36)	123	13 (10)	7.2 (2.7–19.4)	0.58	NS
No	16	6 (37)	20	1 (5)	5.0 (0.1–241.3)	0.18	
EuroSCORE risk							
Low	9	3 (33)	49	7 (14)	3.5 (0.6–18.9)	0.28	NS
Intermediate	20	15 (40)	69	9 (12)	10.2 (2.1–60.2)	0.63	
High	28	12 (43)	25	2 (8)	10.4 (1.8–60.2)	0.88	
Hypothermic CPB							
Yes	18	8 (44)	28	2 (7)	15.2 (2.2–104.0)	0.51	NS
No	39	13 (33)	115	12 (10)	5.5 (1.7–18.1)	0.88	

Odds ratios were adjusted for age, sex, body mass index, preoperative plasma creatinine, left ventricular ejection fraction, EuroSCORE, pulmonary artery hypertension, preoperative insulin treatment, complex surgery, and β-blocker use as appropriate.

CBP = cardiopulmonary bypass; CI = confidence interval; HL = Hosmer Lemeshow; NS = nonsignificant.

Interaction term between the stratification characteristic and insulinoresistant in the multivariate logistic regression model.

cardiac surgery.[8–10,15,31] A beneficial effect of postoperative glycemic control on outcome has been recently demonstrated in diabetic and nondiabetic patients admitted to a surgical intensive care unit, principally after cardiac surgery.[32] Although numerous clinical trials have suggested that intraoperative glycemic control may be rendered difficult during on-pump cardiac surgery,[18,23,33] no study has reported its impact on outcomes after cardiac surgery in diabetic patients. We hypothesized that poor intraoperative glycemic control would be associated with worsened hospital outcome. Hyperglycemia has been previously reported to exert deleterious effects on myocardium subjected to ischemia–reperfusion process,[11,12,14,34,35] and two recent studies have demonstrated that intraoperative adverse myocardial events assessed by early cardiac I troponin release may influence in-hospital as well as long-term outcome after cardiac surgery.[36,37] We found that poor intraoperative glycemic control is associated with an increase in intrahospital severe morbidity. Our findings are consistent with previous studies that reported beneficial effects of tight glycemic control in different clinical settings.[8,10,24,31,32,38] However, the current study is the first to report the real impact of intraoperative glycemic control on in-hospital outcome after cardiac surgery in diabetics patients. Although the current study was purely observational, the available data in the literature allow speculation on underlying mechanisms. As previously mentioned, hyperglycemia has been described to be, in itself, potentially deleterious for myocardium[11,12,14,34,35] and may be responsible for endothelial dysfunction.[14,39] Moreover, the intraoperative refractory hyperglycemia observed in our study suggests a possible insulin resistance, which has been previously reported during cardiac surgery.[40] This phenomenon contributes to an increase in the concentration of in circulating free fatty acids due to increased lipolysis. These compounds are well recognized to be detrimental during ischemic myocardium by inducing increase myocardial oxygen demand, arrhythmias, calcium overload, and myocardial dysfunction.[10,15,41] All of these cardiac adverse effects could contribute to an increase in morbidity in diabetic patients who exhibit poor intraoperative glycemic control despite insulin therapy.

The following points must to be considered in the assessment of the clinical relevance of our study. First, we cannot exclude that more aggressive insulin therapy might normalize intraoperative BGL, although our protocol is in accord with the more recent recommendations[8] and represents a major effort to control BGL. Second, because our study was purely observational, we cannot establish a causal relation between difficult intraoperative glycemic control and an increase in severe in-hospital morbidity. Two hypotheses may be suggested, both of which require further study: (1) poor glycemic control identifies patients at higher risk or (2) is responsible for an increased risk. These two hypotheses may not be mutually exclusive. Third, the power of our study was not sufficient to evaluate the impact of intraoperative glycemic control on mortality. Nevertheless, in the univariate analysis, the overall mortality rate was significantly higher in patients who exhibited poor intraoperative glycemic control.

In conclusion, in treated diabetic patients undergoing on-pump cardiac surgery, the intraoperative glycemic control can be rendered difficult in spite of aggressive insulin therapy. In these patients, the occurrence of a poor intraoperative glycemic control is associated with a worsened hospital outcome.

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Appendix:

Intraoperative Insulin Protocol** The infusion of insulin was initiated according to the following protocol: $<$ 180 mg/dl, 0 U/h; 180–220 mg/dl, 1 U/h; 221–249 mg/dl, 2 U/h; $>$ 249 mg/dl, 3 U/h. Subsequently, blood glucose concentrations were measured every 30 min, and the insulin infusion rate was titrated according the following protocol: $<$ 140 mg/dl, rate of infusion was maintained at 0 until 180 mg/dl. Then, the insulin infusion was restarted at a rate 50% of the previous rate; 140–179 mg/dl, decrease the rate by 0.5 U/h; 180–220 mg/dl, no changes in the infusion rate; 221–249 mg/dl, if the blood glucose concentration was lower than in the last test, the rate of infusion was unchanged, and if the blood glucose concentration was greater than in the last test, the infusion rate was increased by 0.5 U/h; $\geq$ 250 mg/dl, the rate of infusion was increased by 1 U/h. If the blood glucose concentration did not decrease after three successive measures, the insulin infusion rate was doubled.

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