Impact of hyperglycemia on perioperative mortality after coronary artery bypass graft surgery

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Objective: The roles of perioperative hyperglycemia and diabetes in the risk stratification of patients undergoing coronary artery bypass graft surgery are unclear. The aim of this study is to explore the influence of perioperative hyperglycemia on postoperative mortality.

Method: A prospective, observational study of 5050 patients undergoing cardiopulmonary bypass for coronary artery bypass graft surgery at 70 international centers was conducted, with 7500 measured variables per patient and outcomes adjudicated centrally. Postoperative blood glucose levels measured from the day of surgery to postoperative day 3 were available for 4799 patients. Multivariable logistic regression was used to determine the association of hyperglycemia with hospital mortality.

Results: A total of 164 patients died during hospitalization (3.2%). Mortality was significantly higher in the diabetic population compared with the nondiabetic population (4.2% vs 2.9%; $P = .02$). In nondiabetic patients, maximum postoperative blood glucose between 250 and 300 mg/dL (adjusted odds ratio, 2.56; 95% confidence interval, 1.18–5.57; $P = .02$) and maximum blood glucose of 300 mg/dL or greater (adjusted odds ratio, 2.74; 95% confidence interval, 1.22–6.16; $P = .01$), compared with maximum blood glucose less than 200 mg/dL, and postoperative insulin treatment (adjusted odds ratio, 2.04; 95% confidence interval, 1.12–3.70), were independent risk factors for an increased risk of in-hospital mortality. In diabetic patients, hyperglycemia was not associated with a higher mortality risk.

Conclusions: Postoperative hyperglycemia is associated with increased in-hospital mortality in nondiabetic patients after coronary artery bypass graft surgery. In diabetic patients, hyperglycemia was not associated with mortality. (J Thorac Cardiovasc Surg 2011;142:430-7)

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Hyperglycemia commonly occurs in critically ill patients and is associated with increased mortality and morbidity.^{1,2} Postoperative control of hyperglycemia has been shown to improve patient outcome in intensive care units and after cardiac surgery.^{3,4} Hyperglycemia in nondiabetic patients is related to stress hyperglycemia and is a poor sign.⁵ In the era of percutaneous coronary intervention, patients requiring coronary artery bypass graft (CABG) surgery are older and sicker than in past years, with approximately 20% being diabetic. Diabetes was found to be an independent risk factor for in-hospital and long-term mortality after cardiac surgery. Thus, a history of diabetes has been used for risk stratification in cardiac surgery.⁶

After acute myocardial infarction, short-term mortality was predicted by hyperglycemia at admission, whereas long-term mortality was associated with diabetes.⁷ To evaluate the role of hyperglycemia on mortality after CABG surgery, we investigated blood glucose levels using Multicenter Study of Perioperative Ischemia Epidemiology II data. We hypothesized that perioperative hyperglycemia is associated with an increased mortality risk in both diabetic and nondiabetic patients.

Abbreviations and Acronyms

CABG	= coronary artery bypass graft
CI	= confidence interval
CPB	= cardiopulmonary bypass
DOS	= day of surgery
OR	= odds ratio
POD3	= postoperative day 3

MATERIALS AND METHODS**Study Design**

The Multicenter Study of Perioperative Ischemia Epidemiology II is a prospective, longitudinal, observational study that enrolled 5436 patients with coronary artery disease refractory to medication, who were scheduled for CABG surgery at 72 medical institutions among 17 countries in North and South America, Europe, the Middle East, and Asia. After approval from the institutional review board and written patient consent had been obtained at each institution, 100 patients were selected for prospective enrollment according to a systematic sampling scheme. Enrollment eligibility criteria were as follows: scheduled to undergo CABG surgery with the use of cardiopulmonary bypass (CPB), at least 18 years old, able to complete the preoperative interview, and not enrolled in another study or clinical trial. Enrollment commenced in November 1996 and ended in June 2000.

Study Data

For each enrolled patient, approximately 7500 variables were collected from admission through discharge. Demographic, medical history, clinical, laboratory, electrocardiographic, specialized testing, resource use, and adverse outcome data were collected. Data were adjudicated centrally, with all data for each patient examined for completeness and accuracy before database closure on October 15, 2001.

Measurement of Outcomes

All outcomes were prespecified, defined by protocol, and determined by investigators who were not aware of the subsequent planned analysis. Fatal and nonfatal outcomes were classified as cardiac (myocardial infarction or heart failure), cerebral (stroke or encephalopathy), renal (kidney dysfunction or failure), gastrointestinal (ischemia or infarction), or other (eg, adverse events). Perioperative death was defined as any death occurring in the hospital. Diabetic patients were defined as those with previously diagnosed disease at admission.

Clinical Care and Blood Glucose Measurements

Clinical decisions were not controlled by the study protocol. All patients qualifying for enrollment within the prespecified 44-month enrollment period were entered. Of the 5436 patients enrolled, 386 were excluded from analysis because they chose to withdraw (32 patients); died before surgery (2 patients); canceled or rescheduled surgery (97 patients); canceled CPB with CABG surgery (132 patients); inadvertently enrolled in another study (11 patients); had incomplete data (86 patients); had incomplete blood sampling, shipping, or storage of blood (11 patients); or had incomplete data on their diabetes status (15 patients). A total of 5050 patients remained in the study. Maximum blood glucose levels were recorded before surgery (admission and preoperative), during surgery (before, during, and after CPB), and postsurgery (at intensive care unit entry, remaining day of surgery [DOS], postoperative days 1–4, maximum value after postoperative day 4, and last day before discharge). Maximum blood glucose level at admission or preoperatively was categorized as 144 mg/dL or less and greater

than 144 mg/dL.⁸ Maximum blood glucose level during surgery was used as the intraoperative maximum blood glucose level. Maximum blood glucose level between the remaining DOS and postoperative day 3 (POD3) was used as the early postoperative maximum blood glucose level (DOS–POD3 glucose maximum). Study patients were classified as having good, moderate, poor, or very poor glucose control if the DOS–POD3 glucose maximum was less than 200 mg/dL, 200 to less than 250 mg/dL, 250 to less than 300 mg/dL or 300 mg/dL or greater, respectively. The cutoff points were defined on the basis of previous reports in the literature.⁹

Statistical Analysis

Descriptive statistics (mean, standard deviation, median, and interquartile range) were calculated for all continuous variables, including blood glucose levels. For categorical variables, a chi-square or Fisher exact test was used to compare nondiabetic and diabetic patients; for continuous variables, a *t* test or Wilcoxon rank-sum test was applied.

Stratified analysis was conducted to examine the association between hyperglycemia and in-hospital mortality, controlling for the patients' diabetic histories and insulin treatment. Models were repeated using different definitions of hyperglycemia, that is, early postoperative maximum blood glucose 200 mg/dL or greater, 250 mg/dL or greater, or 300 mg/dL or greater.

Patients were evaluated as a group and then reanalyzed after grouping by their history of diabetes. Diabetic patients were further subdivided into 3 groups: insulin-treated diabetes, diet-controlled type 2 diabetes, or oral antidiabetic-controlled type 2 diabetes. We developed a series of multivariable models to individually assess the independent effect of early postoperative maximum blood glucose levels on mortality for the diabetic patients and nondiabetic patients. In addition, the associations between hyperglycemia (DOS–POD3 maximum blood glucose $\geq$ 250 mg/dL) and predictors in nondiabetic patients were examined. Univariate associations between postoperative mortality and a comprehensive list of risk factors (preoperative demographic and medical characteristics, perioperative medications, intraoperative variables, and perioperative laboratory values) were investigated for each group using the chi-square test, Fisher exact test, and logistic regression modeling. Risk factors significant at a nominal 2-sided *P* value of .2 or less were then entered into multivariable logistic regression models using a combination stepwise selection method; the model retention criterion was set at *P* less than .05. The calibration of the logistic models was assessed using the Hosmer–Lemeshow goodness-of-fit test. All statistical analyses were performed using SAS statistical software (version 8.2, SAS Institute Inc, Cary, NC).

RESULTS**Study Population**

Thirty percent of patients had a history of diabetes (type 2 diabetes controlled by diet [5.1% of the whole population], type 2 diabetes controlled with oral antidiabetics [17.4%], or insulin-treated diabetes [7.5%]). Baseline demographics and medical characteristics of all patients are listed in Table 1.

Mortality

A total of 164 of the 5050 patients (3.2%) died during hospitalization in the study period. Eighty-one percent of these deaths were preceded by vascular events: myocardial infarction, congestive heart failure, stroke, or a combination of these. Thirty-eight percent (63/164) of all deaths occurred in patients with diabetes. Overall mortality rates were 3.1%, 3.5%, and 6.4% in the diet-controlled, oral

TABLE 1. Patient characteristics, preadmission comorbidities, preoperative chronic medication, and perioperative parameters: Nondiabetic and diabetic patients*

Characteristic	Total population (n = 5050) no. (%)	Nondiabetic (n = 3535) no. (%)	Type 2 diabetes, diet-controlled (n = 259)		Type 2 diabetes, oral antidiabetic medication (n = 879)		Insulin-treated diabetes (n = 377)	
			No. (%)	P†	No. (%)	P‡	No. (%)	P§
Age > 70 y	1523 (30.2)	1099 (31.1)	91 (35.1)	.17	235 (26.7)	.01	98 (26.0)	.04
Men	4018 (79.6)	2896 (81.9)	210 (81.1)	.73	654 (74.4)	<.001	258 (68.4)	<.001
BMI > 30	1206 (23.9)	727 (20.6)	83 (32.1)	<.001	280 (31.9)	<.001	116 (30.9)	<.001
Medical history								
Hypertension	3396 (67.5)	2226 (63.3)	196 (75.7)	<.001	687 (78.2)	<.001	287 (76.5)	<.001
Pulse pressure (mm Hg)	57.0	55.0	57.5	.05	59.0	<.001	60.5	<.001
	48.5–67.5	47.5–66.0	50.0–68.0		50.0–70.0		52.0–70.0	
Unstable angina	2542 (50.3)	1725 (48.8)	129 (49.8)	.75	491 (55.9)	<.001	197 (52.3)	.20
Myocardial infarction	2596 (52.0)	1783 (50.9)	138 (53.9)	.35	452 (52.1)	.51	223 (60.1)	<.001
Congestive heart failure	1753 (35.0)	1136 (32.3)	91 (35.7)	.27	346 (39.7)	<.01	180 (48.1)	<.001
PTCA	766 (15.2)	509 (14.4)	29 (11.2)	.15	154 (17.6)	.02	74 (19.7)	.006
CABG	305 (6.0)	222 (6.3)	11 (4.3)	.19	50 (5.7)	.51	22 (5.8)	.73
Pulmonary disease	1068 (21.2)	743 (21.1)	48 (18.6)	.34	179 (20.5)	.67	98 (26.1)	.03
Maximum blood glucose on admission or preoperative, mg/dL	111.7	102.0	138.4	<.001	168.0	<.001	196.2	<.001
	94.0–149.5	91.0–118.9	113.8–179.2		128.0–228.8		138.7–259.4	
Additive euroSCORE	4.0	4.0	4.0	.13	4.0	.04	5.0	<.001
	2.0–6.0	2.0–6.0	2.0–7.0		2.0–6.0		3.0–7.0	
Medication used at admission								
Aspirin	2361 (46.8)	1620 (45.8)	126 (48.7)	.38	420 (47.8)	.30	195 (51.7)	.03
Beta-blockers	3146 (62.3)	2262 (64.0)	154 (59.5)	.14	504 (57.3)	<.001	226 (59.9)	.12
ACE inhibitors	2066 (40.9)	1309 (37.0)	114 (44.0)	.02	433 (49.3)	<.001	210 (55.7)	<.001
Calcium channel blockers	1690 (33.5)	1180 (33.4)	88 (34.0)	.84	298 (33.9)	.77	124 (32.9)	.85
Steroids	75 (1.5)	51 (1.4)	3 (1.2)	.71	10 (1.1)	.49	11 (2.9)	.03
Intravenous inotropes	188 (3.7)	121 (3.42)	8 (3.1)	.77	34 (3.9)	.52	25 (6.6)	.002
Epinephrine	2 (0.04)	2 (0.1)	0 (0.0)	>.99	0 (0.0)	>.99	0 (0.0)	>.99
Perioperative characteristics								
Combined valve surgery	552 (10.9)	412 (11.7)	24 (9.3)	.24	83 (9.44)	.06	33 (8.75)	.09
Assist device	225 (4.5)	139 (3.9)	15 (5.8)	.14	40 (4.6)	.40	31 (8.2)	<.001
Use of epinephrine	1242 (24.6)	861 (24.4)	68 (26.3)	.49	210 (23.9)	.77	103 (27.3)	.20
CPB time, min	96.0	95.0	99.0	.23	98.0	.14	100.0	.05
	74.0–124.0	73.0–123.0	77.0–125.0		77.0–123.0		78.0–125.0	
Postoperative minimum hemoglobin, ¶ g/dL	9.0	9.1	9.0	.31	9.0	.87	8.9	.02
	8.2–10.0	8.2–10.0	8.3–9.8		8.2–10.1		8.1–9.8	
Postoperative maximum blood glucose, # mg/dL	201.8	182.0	230.0	<.001	266.0	<.001	305.0	<.001
	164.0–260.0	155.0–218.0	186.0–279.2		224.0–311.0		252.2–360.0	
Postoperative creatinine ≥ 1.4 mg/dL	1669 (33.4)	1086 (31.1)	88 (34.2)	.30	321 (36.8)	.002	174 (46.5)	<.001
Aspirin within the first 48 h after CABG	2992 (59.3)	2122 (60.0)	145 (56.0)	.20	511 (58.1)	.31	214 (56.8)	.22
Postoperative administration of ≥ 3 simultaneous inotropes	513 (10.2)	346 (9.8)	32 (12.4)	.18	86 (9.8)	.99	49 (13.0)	.05
Postoperative use of epinephrine	1143 (22.6)	784 (22.2)	68 (26.3)	.13	191 (21.7)	.77	100 (26.5)	.06
Postoperative use of steroids	286 (5.7)	204 (5.8)	12 (4.6)	.45	46 (5.2)	.53	24 (6.4)	.64

BMI, Body mass index; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; euroSCORE, European System for Cardiac Operative Risk Evaluation; ACE, angiotensin-converting enzyme; DOS, day of surgery; POD, postoperative day. *Categorical variables are summarized by numbers and percentages, and *P* values were calculated by the chi-square or Fisher exact test (as appropriate); continuous variables are summarized by medians and interquartile ranges, and *P* values were calculated by the Wilcoxon rank-sum test. Bonferroni adjustment requires *P* < .016 for significance. †*P* values are for the comparison between nondiabetic patients and type 2 diabetic patients with diet control. ‡*P* values are for the comparison between nondiabetic patients and type 2 diabetic patients using oral antidiabetic medication. §*P* values are for the comparison between nondiabetic patients and type 1 diabetic patients, insulin treated. ||Insertion of intra-aortic balloon pump or ventricular assist device or extracorporeal membrane oxygenation was performed preoperatively, during surgery, or on the remaining DOS. ¶Postoperative minimum hemoglobin was the lowest hemoglobin recorded on the remaining DOS, POD1, POD2, or POD3. #Postoperative maximum blood glucose was the highest maximal blood glucose recorded on the remaining DOS, POD1, POD2, or POD3.

FIGURE 1. Mortality rate and hyperglycemia in nondiabetic patients. The nondiabetic population was divided into 15 equally sized groups according to maximum DOS–POD3 blood glucose level. The x-axis shows the mean maximum blood glucose values of the 15 groups. In-hospital mortality rate and maximum DOS–POD3 blood glucose levels in the nondiabetic population showed a strong linear relationship at blood glucose levels of 200 mg/dL or greater. Numbers above bars indicate percent mortality. Bars indicate standard deviation. *DOS*, Day of surgery; *POD3*, postoperative day 3.

antidiabetic-controlled, and insulin-treated groups, respectively. Mortality was significantly higher in the diabetic population compared with the nondiabetic population (4.2% vs 2.9%; $P = .02$).

Perioperative Glycemic Control

Postoperative blood glucose measurements were available for 4799 patients. In the whole population, blood glucose control was good (glucose maximum <200 mg/dL) in 2358 patients (49.1%), moderate (200–<250 mg/dL) in 1071 patients (22.3%), poor (250–<300 mg/dL) in 679 patients (14.2%), and very poor (≥ 300 mg/dL) in 691 patients (14.4%) in the early postoperative period. In the nondiabetic population, postoperative blood glucose control was good in 2127 patients (64.4%), moderate in 711 patients (21.5%), poor in 282 patients (8.5%), and very poor in 185 patients (5.6%). In the diabetic population, blood glucose control was good in 231 patients (15.5%), moderate in 360 patients (24.1%), poor in 397 patients (26.6%), and very poor in 506 patients (33.9%).

Persistent Hyperglycemia and Administration of Insulin

Postoperatively, 831 (25.1%) of nondiabetic patients were treated with insulin from the DOS to POD3, in comparison with 1261 (84.4%) of the diabetic patients (diet-controlled type 2 diabetes: 59.2%; oral antidiabetic-controlled type 2 diabetes: 87.2%; insulin-treated diabetes: 95.2%). Stratified analysis was performed to examine the association between diabetes and insulin treatment, controlling for the maximum postoperative blood glucose levels on DOS to POD3. At the same blood glucose level, diabetic patients were more likely to be treated with insulin (maximum glucose <200 mg/dL: odds ratio [OR], 11.06; 95% confidence interval [CI],

FIGURE 2. Mortality rate and hyperglycemia in diabetic patients. The diabetic population was divided into 15 equally sized groups according to maximum DOS–POD3 blood glucose level. The x-axis shows the mean maximum blood glucose values of the 15 groups. In the diabetic population, only when glucose levels exceeded 300 mg/dL was there a significant increase in unadjusted mortality compared with lower levels. Numbers above bars indicate percent mortality. Bars indicate standard deviation. *DOS*, Day of surgery; *POD3*, postoperative day 3.

8.23–14.88; $P < .001$; 200–<250 mg/dL: OR, 7.19; 95% CI, 5.37–9.62; $P < .001$; 250–<300 mg/dL: OR, 6.08; 95% CI, 4.13–8.94; $P < .001$; ≥ 300 mg/dL: OR, 5.88; 95% CI, 3.38–10.23; $P < .001$).

Intra- and Postoperative Hyperglycemia and Mortality

The relationship between early postoperative maximum blood glucose levels and mortality rate in the nondiabetic population differed from that in the diabetic population. In the nondiabetic population, the relationship between maximum glucose between DOS and POD3 and mortality rate showed a reasonably linear pattern of greater than 200 mg/dL (Figure 1). In contrast, in the diabetic population, association with an increase in the mortality rate was present only when postoperative maximum blood glucose levels exceeded 300 mg/dL (Figure 2).

Stratified analysis of crude in-hospital mortality rates by hyperglycemia, diabetes, and insulin treatment (on DOS to POD3) status resulted in similar findings. The analysis was repeated using different levels to define control of hyperglycemia: maximum blood glucose on DOS to POD3 200 mg/dL or greater, 250 mg/dL or greater, or 300 mg/dL or greater (Table 2). In nondiabetic patients, hyperglycemia was associated with increased in-hospital mortality, regardless of in-hospital insulin treatment. Although a significant difference in unadjusted mortality was observed in diabetic patients for maximum glucose 300 mg/dL or greater versus maximum glucose less than 300 mg/dL, this difference was not observed in the multivariable logistic regression after adjustment for other independent predictors.

In the final multivariate logistic regression models, the postoperative maximum blood glucose level remained an independent predictor for mortality in the nondiabetic

TABLE 2. In-hospital mortality rate by hyperglycemia and insulin treatment status*

Definition of hyperglycemia	No insulin			Insulin		
	No./total of patients with in-hospital mortality			No./total of patients with in-hospital mortality		
	Hyperglycemia	No hyperglycemia	<i>P</i> †	Hyperglycemia	No Hyperglycemia	<i>P</i> †
Maximum blood glucose ≥ 200 mg/dL						
All patients	15/804 (1.9)	15/1903 (0.8)	.01	100/1637 (6.1)	10/455 (2.2)	<.001
Nondiabetic patients	13/652 (2.0)	13/1822 (0.7)	.006	53/526 (10.1)	5/305 (1.6)	<.001
Diabetic patients	2/152 (1.3)	2/81 (2.5)	.52	47/1111 (4.2)	5/150 (3.3)	.60
Maximum blood glucose ≥ 250 mg/dL						
All patients	8/232 (3.4)	22/2475 (0.9)	.003	80/1138 (7.0)	30/954 (3.1)	<.001
Nondiabetic patients	7/164 (4.3)	19/2310 (0.8)	<.001	41/303 (13.5)	17/528 (3.2)	<.001
Diabetic patients	1/68 (1.5)	3/165 (1.8)	.85	39/835 (4.7)	13/426 (3.1)	.17
Maximum blood glucose ≥ 300 mg/dL						
All patients	2/61 (3.3)	28/2646 (1.1)	.15	57/630 (9.0)	53/1462 (3.6)	<.001
Nondiabetic patients	2/39 (5.1)	24/2435 (1.0)	.06	28/146 (19.2)	30/685 (4.4)	<.001
Diabetic patients	0/22 (0.0)	4/211 (1.9)	>.99	29/484 (6.0)	23/777 (3.0)	.009

*Hyperglycemia was defined on the basis of the maximum blood glucose from the remaining DOS to POD3, using different cutoff levels: maximum blood glucose ≥ 200 mg/dL, ≥ 250 mg/dL, or ≥ 300 mg/dL; insulin treatment was defined as receiving insulin from the remaining DOS to POD3. Percentage is shown in parentheses. †*P* values shown are for the comparison between patients with and without hyperglycemia.

patients. This was not the case in the diabetic population (Table 3). Intraoperative maximum blood glucose levels showed a significant univariate association with mortality in nondiabetic ($P = .02$) but not in diabetic ($P = .95$) patients. In nondiabetic patients, intraoperative blood glucose levels showed no independent relationship with mortality in the multivariate model. When antifibrinolytic agents and early postoperative aspirin were introduced into the model, the relationship between glucose and mortality (and other covariates in the model) remained unchanged.

Risk Factors for Hyperglycemia

In the nondiabetic population, patients with postoperative hyperglycemia (maximum blood glucose DOS–POD3 ≥ 250 mg/dL) had more comorbidities. Preoperative blood glucose level, European System for Cardiac Operative Risk Evaluation risk group, impaired renal function, long duration of CPB, need for assist devices, and need for high inotropic support were significant independent risk factors for hyperglycemia among nondiabetic patients (Table 4).

TABLE 3. Multivariable logistic regression analysis for in-hospital mortality in nondiabetic and diabetic patients*

Risk factor	Nondiabetic population (n = 3535)		Diabetic population (n = 1515)	
	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value
Maximum blood glucose:				
200–<250 vs <200 mg/dL	1.36 (0.65–2.82)	.41		
250–<300 vs <200 mg/dL	2.56 (1.18–5.57)	.02		
≥300 vs <200 mg/dL	2.74 (1.22–6.16)	.01		
Additive euroSCORE†	1.09 (1.01–1.17)	.02	1.12 (1.03–1.22)	.01
Preoperative pulse pressure per 10 mm Hg increment‡	1.36 (1.16–1.60)	<.001		
Assist device§	2.44 (1.30–4.57)	.006	3.87 (1.93–7.79)	<.001
Postoperative administration of ≥ 3 simultaneous inotropes	6.42 (3.65–11.30)	<.001	3.50 (1.86–6.57)	<.001
DOS–POD3 insulin treatment	2.04 (1.12–3.70)	.02		
Postoperative creatinine ≥ 1.4 mg/dL	3.88 (2.06–7.32)	<.001	6.11 (2.66–14.02)	<.001
DOS–POD3 hemoglobin			0.69 (0.52–0.91)	.009

*CI, Confidence interval; euroSCORE, European System for Cardiac Operative Risk Evaluation; DOS, day of surgery; POD, postoperative day. In the model for the nondiabetic population, 262 patients were excluded because of missing values for at least one of the risk factors in the model, including the covariates. The Hosmer–Lemeshow goodness-of-fit chi-square test statistic was 10.47 ($P = .23$). The C-index for the model was .90. In the model for the diabetic population, 18 patients were excluded because of missing values for at least one of the risk factors in the model, including the covariates. The Hosmer–Lemeshow goodness-of-fit chi-square test statistic was 8.82 ($P = .36$). The C-index for the model was .87. †OR was calculated per 1-point increment of additive euroSCORE. ‡OR was calculated per 10 mm Hg increment in preoperative pulse pressure (above a threshold of 40 mm Hg). §Use of intra-aortic balloon pump or ventricular assist device or extracorporeal membrane oxygenation preoperatively, during surgery, or on the remaining DOS. ||DOS–POD3 hemoglobin was categorized per quartile of the lowest hemoglobin value between the day of surgery and the third postoperative day; OR was calculated for quartiles of the hemoglobin value (DOS–POD3).

TABLE 4. Multivariable logistic regression analysis for hyperglycemia in nondiabetic patients

Predictors	Odds ratio (95% CI)	P value
euroSCORE risk group*	1.35 (1.15–1.59)	<.001
Maximum blood glucose (admission or preoperative)†	1.98 (1.43–2.74)	<.001
Creatinine (admission or preoperative) ≥ 1.4 mg/dL	1.45 (1.08–1.93)	.01
Intraoperative administration of ≥ 2 simultaneous inotropes	1.61 (1.26–2.05)	<.001
Assist device‡	3.21 (2.09–4.93)	<.001
CPB time (min)§	1.004 (1.001–1.006)	.006

CI, Confidence interval; euroSCORE, European System for Cardiac Operative Risk Evaluation; CPB, cardiopulmonary bypass. For this analysis, 946 patients (of 3535 nondiabetic patients) were excluded because of missing values for postoperative hyperglycemia or at least one of the predictors in the model, including the covariates. The Hosmer–Lemeshow goodness-of-fit chi-square test statistic was 5.45 ($P = .71$). The C-index for the model was .69. *euroSCORE risk group: low risk, additive euroSCORE 0–3; moderate risk, additive euroSCORE 4–7; and high risk, additive euroSCORE ≥ 8. †OR of maximum blood glucose (admission or preoperative) was calculated as > 144 mg/dL vs ≤ 144 mg/dL. ‡Use of intra-aortic balloon pump or ventricular assist device or extracorporeal membrane oxygenation preoperatively, during surgery, or on the remaining DOS. §OR of CPB time was calculated per 1-minute increment of CPB time.

DISCUSSION

In this large, international, multicenter CABG cohort, we found that the early postoperative, but not the intraoperative, maximum blood glucose level (glucose maximum ≥ 250 mg/dL) was associated with increased in-hospital mortality. This risk was confined to nondiabetic patients. In contrast, hyperglycemia was not associated with higher mortality in diabetic patients after adjustment for other variables. In nondiabetic patients, the direct relationship between mortality and the level of postoperative hyperglycemia persisted regardless of in-hospital insulin treatment. These data suggest that postoperative hyperglycemia is a marker for mortality only in nondiabetic patients. Accordingly, diabetic patients should be separately analyzed in risk stratification.

Acute elevation of blood glucose levels has been found to be associated with increased production of oxygen-derived radicals, decreased complement function, and activation of protein kinase C and nuclear factor κ B.^{10–12} Stress situations, such as surgery and critical illness, induce counter-regulatory hormone release and exacerbate the hyperglycemic state. Because cardiac surgery with CPB produces significant surgical stress, marked elevation of blood glucose levels has frequently been described in patients undergoing cardiac surgery.^{4,9,13} The stress response is more pronounced in unstable hemodynamic conditions, including administration of exogenous catecholamine infusions, use of mechanical assistance devices, and prolonged sedation and ventilation. Stress hyperglycemia in nondiabetic patients was shown to be dependent on the underlying glucose tolerance type, the severity of the disease, and the highly complex interaction of counter-

regulatory hormones.¹³ On the other hand, the proinflammatory effect of hyperglycemia can be reversed by insulin not only in the systemic system but also in the myocardium.¹⁴

According to the recently described metabolic phenomenon,¹⁵ persistent hyperglycemia causes cellular damage and leads to overproduction of reactive oxygen species and thus damages and alters the functions of other parts of the cell, resulting in a continuous overproduction of reactive oxygen species.¹⁰ This oxidative stress persists over a prolonged time, independently of the actual glycemic level, in a self-sustaining manner.¹⁵ Experimental and clinical studies have convincingly established the consequence of metabolic memory, that is, the long-lasting effect of the initial occurrence of poor control of hyperglycemia will cause microvascular complications despite termination of hyperglycemia and reestablishment of good glycemic control later in the treatment.¹⁶ Moreover, a beneficial effect persists if good glycemic control is initiated early, even when followed by poor glycemic control.¹⁶ According to another explanation, chronic hyperglycemia causes cellular conditioning, such as downregulation of glucose transporters, which might be protective against acute hyperglycemia-mediated damage in diabetic patients.⁵ In regard to our findings, we can therefore postulate that poor glycemic control and hyperglycemia itself in the perioperative period caused fewer deleterious consequences in the diabetic patients, because their metabolism had previously been modulated. These hypotheses are supported by the fact that in-hospital insulin treatment was not associated with a decreased risk of mortality. We should emphasize that glycemic control with intravenous insulin to maintain serum glucose less than 180 mg/dL is recommended intraoperatively and postoperatively for at least 24 hours or the duration of intensive care unit stay for patients with and without diabetes undergoing cardiac surgery.⁴ In single-center studies, strict glycemic control reduced mortality in diabetic patients.¹⁷ Therefore, insulin infusion protocols should not be neglected.

Our findings are consistent with previous studies reporting that stress hyperglycemia was more deleterious in patients without a history of diabetes mellitus.^{2,7,18} Although nondiabetic patients were shown to have even lower median glucose values than diabetic patients, their mortality rate was twice as high.¹³ Two meta-analyses for mortality after myocardial infarction² and a study of critically ill patients¹⁹ support the separate investigation of diabetic and nondiabetic populations, when maximum blood glucose levels are included in the analysis. Recent investigations have also indicated that hyperglycemia, but not a history of diabetes, was associated with increased risk of mortality in patients undergoing cardiac surgery⁹ and in critically ill patients.²⁰ Maximum blood glucose levels were associated with increased risk for mortality in nondiabetic patients, but not in the diabetic patients.²⁰ In addition, diabetes is no longer considered an independent risk factor

for in-hospital mortality, as it was 10 years ago,⁶ and diabetic patients have other in-hospital risk factors for mortality. Because diabetic patients undergoing CABG surgery still have both worse short- and long-term survival compared with nondiabetic patients,²¹ a tailored risk estimation and a systematic approach for the treatment of the diabetic population are still lacking. Our findings further confirm the need for the separate analysis of diabetic and nondiabetic patients in risk stratification of CABG surgery.

Considerable numbers of patients can have abnormal glucose metabolism or declining glucose tolerance before the diagnosis of overt diabetes at the time of operation or during hospitalization. As a consequence, the diagnosis of diabetes listed at discharge has dramatically increased. Similar to other reports, our study found that blood glucose levels at admission (which are not always equivalent to fasting blood glucose values) were also an independent predictor of high postoperative maximum blood glucose levels. Admission blood glucose levels were associated with significant morbidity after CABG surgery.²² Our analyses indicated that there is a gradual increase in risk relative to blood glucose levels, regardless of the administration of insulin.

Except for a reduced risk of septicemia, a meta-analysis¹⁹ and a randomized control trial²³ failed to show benefits from tight glycemic control. The occurrence of hypoglycemia was significantly higher in the group under tight glycemic control, and hypoglycemia was independently associated with increased risk for mortality. These results indicate that the goal of maintaining normoglycemia in critically ill patients did not reduce mortality but was associated with an increased risk of hypoglycemia. High blood glucose levels during CPB were found to be independent predictors of mortality after CABG surgery.²⁴ The variability and fluctuation of intraoperative and postoperative blood glucose levels have been found to be associated with increased mortality and morbidity after cardiac surgery.²⁵

It should also be noted that comparison of the results of published studies is difficult, because the definition of hyperglycemia (mean, maximum, or fluctuation of blood glucose levels) and timing of blood glucose sampling vary from one study to another. Also, the definitions of morbidity and the investigated populations were not comparable in most of the studies.

Limitations

Our observations have limitations inherent to the study design. First, the participating investigators in the study had no role in the management of the enrolled patients. Second, there were limited data available for diabetes-specific variables, for example, the amount of insulin administered and the type of oral antidiabetic used. Only a history of diabetes was used for patient categorization. Hemoglobin A_{1c} was not investigated, and preoperative blood glucose levels were not used in the classification of diabetes status. The study

did not regulate the institutional protocols for insulin treatment, cardioplegia, or type of blood glucose measurement.

CONCLUSIONS

Our observations strongly suggest that hyperglycemia, in the absence of a history of diabetes, was independently associated with in-hospital mortality after CABG surgery and that this effect was independent of in-hospital insulin treatment. Postoperative hyperglycemia was not associated with an increased risk of mortality in the diabetic population. Our results also indicate that diabetic and nondiabetic patients should be considered separately in risk stratification.

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APPENDIX E1

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