Prevalence and Clinical Outcome of Hyperglycemia in the Perioperative Period in Noncardiac Surgery

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OBJECTIVE — Hospital hyperglycemia, in individuals with and without diabetes, has been identified as a marker of poor clinical outcome in cardiac surgery patients. However, the impact of perioperative hyperglycemia on clinical outcome in general and noncardiac surgery patients is not known.

RESEARCH DESIGN AND METHODS — This was an observational study with the aim of determining the relationship between pre- and postsurgery blood glucose levels and hospital length of stay (LOS), complications, and mortality in 3,184 noncardiac surgery patients consecutively admitted to Emory University Hospital (Atlanta, GA) between 1 January 2007 and 30 June 2007.

RESULTS — The overall 30-day mortality was 2.3%, with nonsurvivors having significantly higher blood glucose levels before and after surgery (both $P < 0.01$) than survivors. Perioperative hyperglycemia was associated with increased hospital and intensive care unit LOS ($P < 0.001$) as well as higher numbers of postoperative cases of pneumonia ($P < 0.001$), systemic blood infection ($P < 0.001$), urinary tract infection ($P < 0.001$), acute renal failure ($P = 0.005$), and acute myocardial infarction ($P = 0.005$). In multivariate analysis (adjusted for age, sex, race, and surgery severity), the risk of death increased in proportion to perioperative glucose levels; however, this association was significant only for patients without a history of diabetes ($P = 0.008$) compared with patients with known diabetes ($P = 0.748$).

CONCLUSIONS — Perioperative hyperglycemia is associated with increased LOS, hospital complications, and mortality after noncardiac general surgery. Randomized controlled trials are needed to determine whether perioperative diabetes management improves clinical outcome in noncardiac surgery patients.

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P atients with diabetes are more likely to undergo surgery than are those without diabetes (1,2). Surgery in diabetic patients is associated with longer hospital stay, higher health care resource utilization, and greater perioperative mortality than in nondiabetic subjects (1–3). The higher morbidity and mortality in diabetic patients relates in part to the heightened incidence of comorbid conditions including coronary heart disease, hypertension, and renal insufficiency (4,5), as well as the adverse effects of hyperglycemia in clinical outcome (6–8). Evidence from observational studies suggests that in surgical patients, with and without diabetes, improvement in glycemic control positively affects morbidity and mortality (9,10). The stronger body of evidence comes from the setting of cardiac surgery and critically ill patients admitted to the intensive care unit (ICU). In this setting, perioperative hyperglycemia is associated with an increased rate of deep sternal wound infections, hospital complications, and mortality (11,12), and improvement of glycemic control reduces the rate of postoperative complications, length of hospital stay, and mortality (8,12,13). Similarly, the development of perioperative hyperglycemia has also been shown to be a sensitive predictor of nosocomial infection in small observational studies in general surgery (9,10,14). Few studies, however, have reported on the association between glucose levels and hospital mortality in general surgery patients, and it is not known whether the severity of hyperglycemia and the timing of hyperglycemia before or during the postoperative period lead to the increased mortality and hospital complications. Accordingly, the aim of this study was to determine *1*) the relationship between perioperative hyperglycemia and diabetes on clinical outcome (length of hospital stay, need for ICU care, infectious complications, acute renal failure [ARF], respiratory failure, and myocardial infarction) and *2*) the impact of perioperative hyperglycemia on survival after adjustment for known prognostic factors in patients undergoing general noncardiac surgery. We hypothesized that general surgery patients with perioperative hyperglycemia would experience higher hospital complications and mortality compared with patients with normal glucose levels.

RESEARCH DESIGN AND METHODS — Medical records from all patients who underwent inpatient noncardiac surgical procedures at Emory University Hospital, a tertiary academic center in Atlanta, Georgia, between 1 January 2007 and 30 June 2007 were included in the analysis. The patient list was obtained from the operative room electronic medical records. We included patients from general surgery, neurosurgery, surgical oncology, orthopedic, vascular, thoracic, urology, otolaryngology (except tonsillectomy), and gynecology

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services. Only the first surgical procedure was included in patients with more than one surgical procedure. We excluded patients with outpatient surgical procedures or those with a length of stay (LOS) <24 h or with minor surgical procedures including endoscopic procedures and ophthalmologic surgery. The study was approved by the Emory University Institutional Review Board.

We collected data on demographics, LOS, 30-day mortality rate, inpatient laboratory values such as whole blood glucose, plasma blood glucose, and creatinine 1 day before, 1 day after surgery (postsurgery day 1), and within the first 10 days after surgery. Diabetes was defined by ICD-9 codes (250). Hospital complications including myocardial infarction (410.51, 410.71, 410.81, and 410.91), pneumonia (481, 482, 485, and 486), sepsis and bacteremia (0.38, 790.7, 785.52, and 995.9), skin infection (681, 682, 685, 686, and 707), and urinary tract infection (599.0 and 590.8) were identified. ARF was defined as an increase in serum creatinine >0.5 mg/dl from baseline during the hospital stay. Mortality rate was assessed in the hospital and within a 30-day period after surgery. The 30-day mortality was captured using hospital records, outpatient medical records, and the database from the National Surgical Quality Improvement Program.

Severity of surgery was graded as low, intermediate, and high based on American College of Cardiology/American Heart Association preoperative evaluation guidelines (15). High-risk procedures included aortic and other major vascular and peripheral arterial surgical procedures. Intermediate risk procedures included carotid endarterectomy and head and neck, intraperitoneal and intrathoracic, orthopedic, and prostate surgical procedures. Low-risk procedures included superficial procedures (procedures involving skin, skeletal muscle, or superficial fat) and breast surgery.

Data analysis
Comparison of baseline demographics and clinical characteristics between groups were analyzed by nonparametric Wilcoxon tests for continuous variables. For categorical variables, χ^2 tests were used. Multiple logistic regression and adjusted odds ratios were used to determine the influence of covariates including demographic and clinical characteristics on mortality rates. Multivariate linear regression was used to study the effects of these

Table 1—Patient characteristics

Variable	All	Nondiabetic	Diabetic	P value
n	3,112	2,469 (80)	643 (20)	
Age (years)	56.5 ± 16	55.4 ± 15.9	61.2 ± 13.2	<0.001
Sex				
Female	1,712 (53.8)	1,404 (55.2)	308 (47.9)	<0.001
Male	1,472 (46.2)	1,137 (44.8)	335 (52.1)	<0.001
BMI (kg/m^2)	27.6 ± 7.3	26.8 ± 6.9	29.6 ± 7.8	<0.001
Race				
Caucasian	2,161 (71.5)	1,756 (73.2)	405 (65.2)	n.s.
African American	693 (23)	514 (21.4)	179 (28.8)	<0.001
Hispanic	40 (1.3)	32 (1.3)	8 (1.9)	<0.001
Severity of surgery				
Low risk	268 (8.4%)	224 (8.8)	44 (6.8)	n.s.
Moderate risk	2,707 (85%)	2,165 (85.2)	542 (84.3)	n.s.
High risk	209 (6.6%)	152 (6)	57 (8.9)	0.012
Blood glucose before surgery (mg/dl)	120.4 ± 37.9	112.6 ± 28.2	144.7 ± 51.3	<0.001
Blood glucose on the day of surgery (mg/dl)	137.6 ± 33	132.2 ± 27.6	154.6 ± 41.8	<0.001
Average blood glucose after surgery (mg/dl)	119.9 ± 26.5	114.5 ± 21.2	139.3 ± 33.8	<0.001
Hospital LOS (days)	7.4 ± 10.8	7 ± 10.8	8.8 ± 10.6	<0.001
Mortality at 30 days	72 (2.26)	52 (2.05)	20 (3.11)	n.s.

Data are n (%) or means ± SD.

covariates on LOS. $P < 0.05$ was considered significant.

RESULTS — The original data file consisted of 3,588 medical records. We excluded 374 patients with multiple admissions and 30 patients aged ≥90 years. The patient population included 3,184 patients, 53.8% female and 46.2% male, with mean ± SD age 56.5 ± 16 years and BMI 27.6 ± 7.3 kg/m^2, who underwent noncardiac surgical procedures. Table 1 shows the clinical characteristics of study patients divided into diabetics and nondiabetic patients. A history of diabetes before admission was known in 643 patients (20.2%). Compared with subjects without a history of diabetes, patients with diabetes were older (61.2 ± 13.2 vs. 55.4 ± 15.9 years, $P < 0.001$), had higher BMI (29.6 ± 7.8 vs. 26.8 ± 6.9 kg/m^2; $P < 0.001$), were more likely to be male (52.1 vs. 44.8%; $P < 0.001$), were of minority ethnic groups (African Americans 28.8 vs. 21.4%; $P < 0.001$), and were more likely to undergo high-risk surgical procedures (8.9 vs. 6%; $P = 0.012$).

The blood glucose level before surgery in the entire cohort was 120 ± 38 mg/dl. Of note, there were no significant differences in blood glucose concentration between patients included in and

those excluded from the analysis. As expected, nondiabetic subjects had lower presurgery blood glucose levels (113 ± 28 mg/dl) than patients with a known history of diabetes (145 ± 51 mg/dl; $P < 0.001$). The blood glucose level on the 1st day after surgery was 155 ± 42 mg/dl in diabetic patients and 132 ± 28 mg/dl in nondiabetic subjects; both values were higher than those reported during the subsequent hospital stay (139 ± 34 and 115 ± 21 mg/dl, respectively; $P < 0.01$). After surgery, 40% of patients had mean blood glucose >140 mg/dl; three-fourths of these had mean blood glucose between 141 and 180 mg/dl, and the remainder had blood glucose >180 mg/dl. Clinically significant hyperglycemia (defined as blood glucose >180 mg/dl) was observed in 7.9% of patients before surgery, in 17.2% of subjects on the day of surgery, and in 9.9% of patients during the postoperative period (days 2–10).

Mortality and in-hospital complication rates in patients with and without diabetes are shown in Fig. 1. The overall 30-day mortality was 2.3% (72 of 3,112 patients), with a higher mortality (3.1%) observed in diabetic than in nondiabetic (2.1%) patients, but this difference did not reach statistical significance ($P = 0.105$). Compared with nondiabetic subjects, diabetic patients had a higher rate of
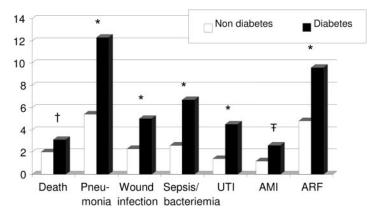
Figure 1—*Thirty-day mortality and in-hospital complication rates in patients with and without diabetes: blood infection (combined bacteriemia and sepsis); urinary tract infection (UTI), acute myocardial infarction (AMI), and ARF. *P < 0.001; †NS; ‡P < 0.017.*

complications including pneumonia (12.1 vs. 5.4%; P < 0.001), wound and skin infections (5 vs. 2.3%; P < 0.001), systemic blood infection (3.6 vs. 1.1%; P < 0.001), urinary tract infections (4.5 vs. 1.4%; P < 0.001), acute myocardial infarction (2.6 vs. 1.2%; P = 0.008), and ARF (9.6 vs. 4.8%; P < 0.001). In addition, diabetic patients had higher length LOS and ICU LOS than nondiabetic subjects (8.8 ± 10.6 vs. 7 ± 10.8 days; P < 0.001 and 2.3 ± 6.2 vs. 1.8 ± 6.5 days; P < 0.01, respectively).

The association between glucose levels before and after surgery and mortality odds ratios is shown in Fig. 2. We found a strong association between mortality and glucose levels both before surgery (Fig. 2A) and after surgery (Fig. 2B); however, mortality odds ratios were different between patients with and without diabetes. The risk of death increased in proportion to blood glucose levels in patients without a history of diabetes (P < 0.001), but the association of hyperglycemia and mortality was greater in patients without a history of diabetes before admission (P < 0.001 for both preoperative and postoperative blood glucose) compared with patients with known diabetes (P = 0.78 for preoperative blood glucose and P = 0.51 for postoperative blood glucose). Multivariate analysis adjusted for age, sex, race, and surgery severity showed that before surgery blood glucose may be an independent predictor of mortality with marginal significance (P = 0.063) and likewise with postoperative blood glucose concentration (P = 0.087). To investigate the effect of race on mortality and hospital complications, we included African American race in the multivariate analyses, which adjusted for age, African Amer-

ican race, diabetes status, interaction between African American race and diabetes, sex, severity of surgery, and presurgery blood glucose levels. We observed

that African American patients were not at increased risk of mortality compared with other races (P = 0.96), but they were more likely to develop complications including pneumonia (P = 0.0075) and ARF (P = 0.0158) than non–African Americans. We observed no difference in blood glucose concentration between racial groups before or after surgery.

The clinical characteristics of survivors and nonsurvivors are shown in Table 2. Compared with survivors, patients who died had significantly higher blood glucose concentrations before surgery (133.4 ± 40.9 vs. 119.9 ± 37.7 mg/dl; P = 0.002) and after surgery (126.6 ± 23.7 vs. 119.7 ± 26.6 mg/dl; P < 0.001). In addition, compared with survivors, deceased patients were older (P < 0.001), the majority of them were men (P < 0.001), they had longer hospital LOS (18 ± 24 vs. 7 ± 10 days; P < 0.001), and they had higher rates of ARF (30.6 vs.
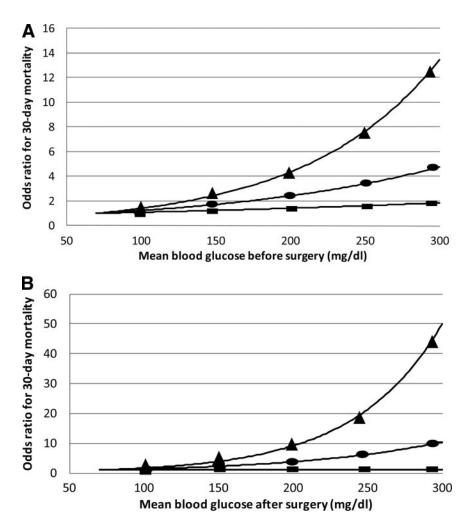

Figure 2—*Mean blood glucose concentration before (A) and after surgery (B) and odds ratio for 30-day mortality in patients with and without diabetes. ●, all patients; ■, diabetic patients; ▲, nondiabetic patients.*

Table 2—*Clinical characteristics of survivors and nonsurvivors*

Variable	Survivors	Nonsurvivors	P value
n	3,112 (98.1)	72 (1.9)	
Age (years)	56 ± 16	65 ± 14	<0.001
Sex: male/female (%)	46/54	67/33	<0.001
Blood glucose (mg/dl)			
Before surgery	118 ± 38	132 ± 42	<0.001
Day of surgery	138 ± 32	143 ± 28	0.028
After surgery (days 2–10)	122 ± 28	130 ± 27	0.007
ARF	163 (5.2)	22 (30.5)	<0.001
Pneumonia	194 (6.2)	22 (30.5)	<0.001
Sepsis	95 (3)	14 (19.4)	<0.001
Acute myocardial infarction	65 (2)	7 (9.7)	<0.001
Hospital LOS (days)	7.2 ± 10.8	18 ± 24	<0.001
ICU LOS (days)	1.8 ± 6.4	14.7 ± 23	<0.001

Data are *n* (%) or means ± SD.

5.2%; $P < 0.001$) and bacteremia/sepsis (16.7 vs. 2.2%; $P < 0.01$). In addition, we found that age, male sex, development of hyperglycemia before or after surgery, blood infections, and acute myocardial infarction were predictors of 30-day mortality.

CONCLUSIONS — Our study indicates that perioperative hyperglycemia is associated with increased risk of hospital complications in patients undergoing noncardiac surgery. Perioperative hyperglycemia significantly increased the risk of pneumonia, systemic blood infections, urinary tract infection, skin infections, and ARF during the postoperative period. In addition, we found a significant association between blood glucose concentration and mortality; however, the impact of hyperglycemia on mortality rate was more significant among patients without a history of diabetes compared with those with known diabetes before admission.

The association between hyperglycemia and increased risk of hospital complications and mortality in critically ill (1,8,12,13) patients undergoing major cardiovascular surgery (12,16,17) is well established. Less information is available on the significance of hyperglycemia in those undergoing general and noncardiac surgery. Small observational studies in noncardiac surgery patients have reported that postsurgical hyperglycemia is associated with infectious complications in general surgery patients (10). In patients with hyperglycemia (blood glucose >220 mg/dl) on postoperative day 1, the infection rate was 2.7 times that observed (31.3 vs. 11.5%) in diabetic patients with all serum glucose values <220 mg/dl

(10). When minor infection of the urinary tract was excluded, the relative risk for "serious" postoperative infection (sepsis, pneumonia, and wound infection) increased to 5.7 when any postoperative day 1 blood glucose level was >220 mg/dl. Ramos et al. (14) showed an increase in postoperative infection rate by 30% for every 40 mg/dl rise in postoperative blood glucose levels >110 mg/dl and increased length of hospital stay in general and vascular surgery patients independent of their diabetes status. The results of our study confirm the association between increased length of hospital stay and risk of hospital complications and mortality in patients with blood glucose levels >150 mg/dl, particularly in those who did not have a prior diagnosis of diabetes (7,18). We and other investigators (7,19–21) reported previously that the development of hyperglycemia in hospitalized patients without a history of diabetes is an important outcome marker associated with worse clinical outcome compared with that of those with a previous history of diabetes or with normoglycemia.

To investigate the effect of race on mortality and hospital complications, we included African American race in the multivariate analyses, which adjusted for age, diabetes status, sex, severity of surgery, and glucose levels. We observed that African American patients had mortality rates similar to those of other races ($P = 0.96$), but they were more likely to develop complications including pneumonia ($P = 0.0075$) and ARF ($P = 0.0158$) than non–African Americans. We observed no difference in blood glucose concentration among racial groups before or after surgery;

thus, the observed difference in hospital complications cannot be explain by differences in glycemic control among racial groups. This observation needs to be confirmed in future studies in different inpatient clinical settings with particular attention to severity of illness and presence of comorbidities. The reasons for poor outcome with high blood glucose levels remain unclear. Much of the attention has focused on increased rate of infections and poor wound healing (1,22). Hyperglycemia is associated with impaired leukocyte function, including decreased phagocytosis, impaired bacterial killing, and chemotaxis (23). Hyperglycemia has also been shown to impair collagen synthesis and to impair wound healing among patients with poorly controlled diabetes (22). Acute hyperglycemia activates the oxidative pathway through increased generation of reactive oxygen species. Reactive oxygen species cause direct tissue damage by lipid oxidation and neutralize nitric oxide, which impairs vasodilation and reduces tissue perfusion (24). The proinflammatory pathway is also activated through nuclear factor-κB activation. This leads to production of inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and plasminogen activator inhibitior-1, which causes increased vascular permeability and leukocyte and platelet activation (24). Similarly, acute hyperglycemia and oscillating glucose levels have been shown to cause higher levels of oxidative stress and endothelial dysfunction than chronic and sustained hyperglycemia (25).

The main limitation of this study is its retrospective nature. Our study did not address the question of whether treatment of hyperglycemia may reduce hospital complications or mortality during the perioperative period. Although several prospective randomized trials in patients undergoing coronary bypass surgery have shown that aggressive glycemic control reduces short- and long-term mortality and systemic infections, it is not clear whether intensified insulin therapy in general surgery will improve clinical outcome and lower mortality. Our group is currently conducting a prospective, randomized trial of strict glycemic control to address these issues.

In summary, perioperative hyperglycemia is associated with increased in-hospital morbidity, hospital and ICU

LOS, and mortality. Hyperglycemia as well as age, sepsis, pneumonia, ARF, and acute myocardial infarction were other important predictors of mortality. These results suggest that hyperglycemia is harmful and should be treated during the perioperative period in general surgical patients. The fact that patients without a history of diabetes (stress hyperglycemia) experience worse outcome and higher mortality at a glucose level the same as that for those with a known history of diabetes suggests a lack of adaptation to acute hyperglycemia and its associated inflammatory and oxidative state. Our results underscore the need for prospective trials to assess the impact of glycemic control during the perioperative period in surgery patients.

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