Perioperative Glycemic Control and the Risk of Infectious Complications in a Cohort of Adults With Diabetes

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OBJECTIVE — Although hyperglycemia is hypothesized to increase the short-term risk of infection, this hypothesis has not been well tested in a clinical setting. This study was designed to assess the relationship of perioperative glycemic control to the subsequent risk of infectious complications.

RESEARCH DESIGN AND METHODS — A total of 411 adults with diabetes who underwent coronary artery surgery from 1990 to 1995 in the cardiac surgery service of an urban university hospital were included in a nonconcurrent prospective cohort study based on chart review. Perioperative glycemic control was characterized by the mean of six capillary glucose measurements taken during the 36-h interval following surgery. The major outcomes studied were infections of leg and chest wounds, pneumonia, and urinary tract infections.

RESULTS — Mean postoperative glucose levels ranged from 121 to 352 mg/dl and were divided into quartiles: quartile 1 (121–206 mg/dl), quartile 2 (207–229 mg/dl), quartile 3 (230–252 mg/dl), and quartile 4 (253–352 mg/dl). After simultaneous adjustment for age, sex, race, underlying comorbidity, acute severity of illness, and the length of the stay in the surgical intensive care unit, patients with higher mean capillary glucose readings were at increased risk of developing infections. Compared with people in the lowest quartile of postoperative glucose, those in quartiles 2 (relative odds of infection [95% CI] = 1.17 [0.57–2.40]), 3 (1.86 [0.94–3.68]), and 4 (1.78 [0.86–3.47]) were at progressively higher risk for infection ($P = 0.05$ for trend).

CONCLUSIONS — In patients with diabetes who undergo coronary artery surgery, postoperative hyperglycemia is an independent predictor of short-term infectious complications. Physicians should consider a glucose concentration target of ≤200 mg/dl to reduce the risk of infection.

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It is well established that individuals with diabetes are at higher risk than their nondiabetic counterparts for a variety of bacterial infections such as cystitis, cellulitis, and postoperative wound infections (1). Less certain is the explanation for this excess risk. Possible explanations fall into two major categories: *1*) those directly related to hyperglycemia via short-term effects on immune function, pathogen growth, or vascular permeability and *2*) those indirectly related to hyperglycemia (and other diabetes-related metabolic abnormalities) via long-term effects on the microvascular system (2,3).

The distinction between these two classes of pathophysiologic mechanisms has immediate implications for the care of the 3.5 million individuals with diabetes who are hospitalized annually in the U.S. (4), particularly those undergoing surgery. The hospital stay for major surgery represents a brief high-risk interval for bacterial infection related to transient compromise of host defenses (e.g., penetration of sterile spaces by surgical dissection and by endotracheal tubes and urinary catheters; suppression of gag reflex by anaesthesia). It also presents an opportunity for implementing unusually strict glycemic control, facilitated by frequent monitoring and the presence of 24-h nursing care. If the excess risk of postoperative infection in diabetic individuals were related to short-term effects of hyperglycemia, then strict perioperative glycemic control might reduce this risk. If, instead, their excess risk is related indirectly to glycemic control via its long-term connection with microvascular disease, then the disadvantages of strict control (i.e., increased risk of significant hypoglycemia, added costs related to monitoring) might outweigh any potential benefits.

Although numerous in vitro studies of glucose's adverse effects on immune function have been published (5–9), only four previous studies have investigated the short-term effects of hyperglycemia on infection risk in a clinical setting (10–13). These four studies provided mixed results: only one found evidence that perioperative hyperglycemia predicted the subsequent occurrence of in-hospital complications (10); the other three did not (11–13). Moreover, these studies were limited by failure to account for potentially confounding factors such as underlying comorbidity (11–13), postoperative severity of illness (10–13), or secular trends in perioperative care (10). Nonetheless, many experts recommend that perioperative blood glucose concentrations be held <200 mg/dl, largely on the strength of the in vitro studies (14–17). With this recommendation in mind, we conducted a non-concurrent, prospective cohort study to assess the independent relationship between perioperative glycemic control and the subsequent risk of infectious complications in diabetic inpatients undergoing coronary artery surgery.

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Abbreviations: APACHE III, Acute Physiology and Chronic Health Evaluation III.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Participants

Patients with diabetes (regardless of diabetes subtype) who underwent coronary artery bypass surgery at Johns Hopkins Hospital from 1 January 1990 through 31 December 1995 were identified from a surgical log. Of the 576 patients so identified, inpatient records of 510 patients were available for review. Patients were excluded if they had missing data (primarily, fewer than three capillary glucose readings on each postoperative day, $n = 72$); infectious complications within 36 h of surgery ($n = 20$); evidence of preoperative infection such as a positive culture, infiltrate, or use of antibiotics on admission ($n = 5$); or death within 36 h of surgery ($n = 2$). The remaining 411 patients became the subjects of our study. Patients who had missing data or whose charts were not available for review, were similar to the study cohort in terms of sex (56 vs. 54% male) and race (84 vs. 81% Caucasian; both $P > 0.1$). However, excluded patients did tend to be slightly older (65 vs. 63 years; $P = 0.01$), compared with the study cohort.

Data source and collection

The source for all data was existing medical records related to the hospitalization for coronary artery surgery. Using data abstraction forms, trained reviewers collected information on demographic characteristics, previous medical history, laboratory results, and clinical events surrounding the surgery. To minimize information bias, data on the main exposure of interest (capillary glucose measurements) were abstracted from the medical record before data were collected on the main outcome (infectious complications).

Demographics and diabetes history

Age, race, and sex of each patient were recorded from the administrative portion of the inpatient chart, as were the admission and discharge dates. In all 411 patients, the presence of diabetes before hospital admission was confirmed by documentation in the admission note, emergency room note, admission orders, nursing database, or discharge summary, or by the prescription of antidiabetic medications in the admission orders.

Comorbidity and severity of illness

The presence of comorbid conditions was assessed using the Charlson Comorbidity Index (18) based on information in the past medical history section of the admission note and in the problem list of the patient's discharge summary. For example, an individual with a prior history of diabetes, a myocardial infarction, and moderate to severe renal disease would receive a score of $1 + 1 + 2 = 4$. As an indicator of diabetes severity, the results of the preoperative urine dipstick for protein was recorded for the 375 patients on whom it was performed. To enhance the specificity of this single measurement on an untimed specimen, the result was dichotomized, with a urine protein $\geq 2+$ classified as positive. Overall severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation III [APACHE III] Prognostic System (19) based on information obtained from the nursing database and based on laboratory work on transfer to an intensive care step-down unit, which typically occurred 12–24 h after surgery. The APACHE III score is an established predictor of in-hospital mortality in critically ill patients (19). The score is a function of the following variables: temperature, heart rate, mean blood pressure, respiratory rate, arterial pH and P_{CO_2} and P_{O_2}, sodium, blood urea nitrogen, creatinine, glucose, leukocyte count, hematocrit, total bilirubin, albumin, urine output, and neurological status. Data on arterial pH, P_{CO_2}, P_{O_2}, albumin, and total bilirubin were assumed to be normal unless otherwise indicated (20).

Postoperative nutrition and diabetes management

Patients followed a coronary artery bypass postoperative protocol (critical pathway) such that they were fed only by nasogastric tube the day of surgery, then given clear fluids on postoperative day 1, and begun on solids on postoperative days 2 or 3. Patients were maintained on a sliding scale of insulin until they were consistently taking solid foods, which was usually on postoperative day 4.

Blood glucose measurements

Glycemic control was characterized using capillary blood glucose measurements that were routinely ordered four times daily (at 7:00 A.M., 11:30 A.M., 4:30 P.M., and 9:00 P.M.) following surgery. Individuals with <3 measurements spaced at least 4 h apart on any single postoperative day were excluded ($n = 72$). To ensure uniform assessment, additional glucose measurements (plasma, serum, or capillary blood) made between routine capillary blood glucose measurements were ignored. Compilation of capillary blood glucose data began immediately following surgery (typically the 4:30 P.M. and 9:00 P.M. measurements were made on the day of surgery) and continued for 7 full days (or until discharge or death). Thus, the number of capillary blood glucose measurements per individual ranged from 6 (for patients who developed infectious complications immediately following the first 36 h postoperatively) to 30 (for patients who remained complication-free up to postoperative day 7). There was an in-hospital quality control system for assessing the accuracy of capillary glucose readings. Every 24 h, two levels of controls were run, a low-normal control and an upper limit control (250–300 mg/dl). Every 3 months, a lab sample was sent to each nursing unit to be correlated with the capillary glucose measurements. Since glucose measurement on admission to the hospital was not standardized with regard to time of day, and since glycohemoglobin assays were only performed on a minority of participants (20%), no measure of preoperative glycemic control was included in the analysis.

Outcomes

A patient was classified as having developed a postoperative infection if any one of the following conditions developed on postoperative day 2 or later (i.e., ≥ 36 h following surgery): *1*) pneumonia (defined by positive sputum culture or new infiltrate on chest radiograph), *2*) urinary tract infection (defined by positive urine culture or pyuria), *3*) wound infection (defined by positive wound culture, dehiscence, drainage, or cellulitis), or *4*) other infection (defined by other positive culture or addition of new antibiotics prompted by fever). For individuals who had two or more infections, only the first was considered in calculating incidence. Data on postoperative death were also recorded. Outcomes were assigned to a postoperative day if the first supporting evidence was documented in the chart between 12:00 A.M. and 11:59 P.M. on that day. The first full hospital day after surgery was defined as postoperative day 1.

Analysis

Most analyses were conducted using a prospective approach in which the independent variable was perioperative glucose concentration (mean of 6 measurements taken through the end of postoperative day 1) and the dependent variable was subsequent infectious complication. In the

absence of unequivocally significant clinical categories for perioperative glucose concentration, this variable was grouped into quartiles. In unadjusted analyses, 95% CIs around incidence rates were calculated based on the binomial distribution. Next, logistic regression models were used to determine the relative odds (and 95% CIs) of infection by glucose quartile (entered as a set of three indicator variables) after simultaneous adjustment for demographic and clinical characteristics that were thought to represent potential confounders. To test the hypothesis of a graded relationship between glucose concentration and risk of infectious complication, we also performed trend tests in which the *P* value corresponded to a Wald test for glucose concentration entered into the corresponding logistic model as a continuous variable. A subsidiary analysis was also performed in which infectious complications occurring on postoperative day 2 were censored to create a 24-h lag between the assessment of exposure and outcome.

Additional analyses were conducted using a retrospective approach in which the independent variable was case-control status (infectious complication versus none) and the dependent variable was mean postoperative glucose concentration cumulative up to 11:59 P.M. on the day before case-control status was assessed. To examine trends in glycemic control over time, these analyses were repeated for postoperative days 1–7. Thus, individuals who developed infections on postoperative day 2 or later (n = 79) are compared with individuals who were alive and in hospital on postoperative day 3, but who did not develop infection at any point in their hospital stay (n = 307). We used a mean of the 2 capillary glucose measurements taken on the day of surgery and the 4 taken on postoperative day 1 (2 + 4 = 6 measurements in total). At later postoperative days, the number of cases and controls declined—due to death, discharge, and (in cases only) censoring related to prior infection—but the number of glucose measurements that contribute to the cumulative mean increased (by 4 per day), thereby stabilizing the variance of mean glucose over time. Cumulative means (with SEM) for cases and controls on day x + 1 were plotted on day x (i.e., the final day of accumulation before the day of infection). The statistical significance of each case-control comparison was determined by t testing, using separate tests for each postoperative day. A total of 25 patients who were excluded from the prospective analyses because they developed infections during postoperative day 1 were included in the retrospective analyses.

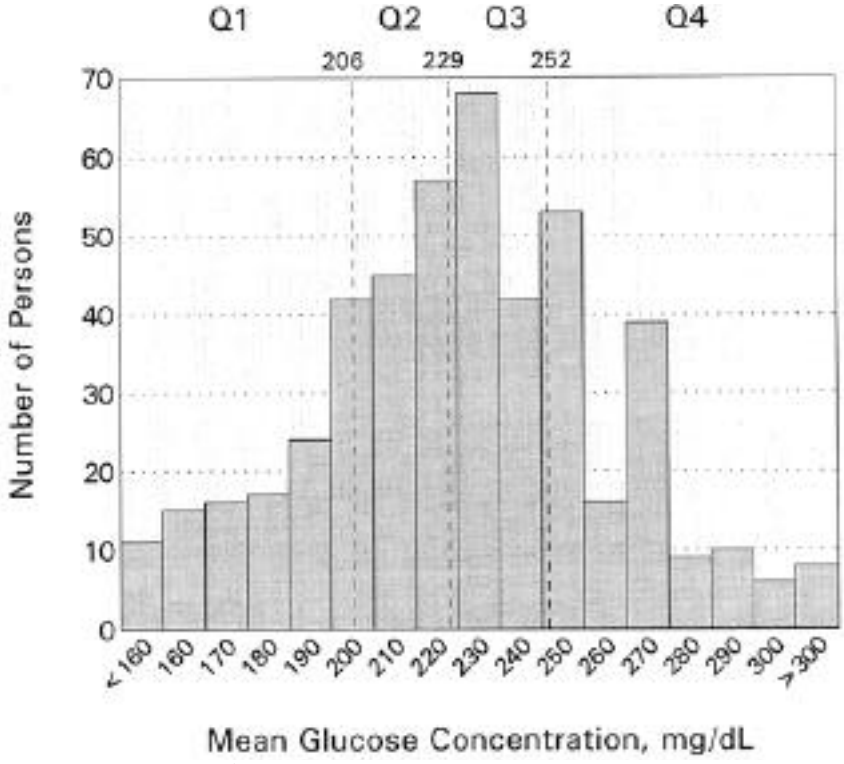

Figure 1—*Distribution of mean perioperative glucose concentration in 411 patients with diabetes who underwent coronary artery surgery. The mean glucose concentrations in milligrams per deciliter represent the average of six capillary glucose readings in the first 36 h postoperatively. The bars represent the number of patients who have a given mean value. The 25th, 50th, and 75th percentiles were 206, 229, and 252, respectively.*

RESULTS

Perioperative glycemic control

Figure 1 displays the distribution of the means of the first 6 capillary glucose measurements through postoperative day 1 (i.e., the 36-h interval following surgery). The median was 229 mg/dl with a range of 121–352 mg/dl. For the purpose of analysis, the distribution was divided into quartiles and patients in quartiles 2 to 4 were compared with those in quartile 1 in assessing for risk of infection. Ranges for each quartile were as follows: quartile 1 (121–206 mg/dl), quartile 2 (207–229 mg/dl), quartile 3 (230–252 mg/dl), and quartile 4 (253–352 mg/dl).

Other baseline characteristics

Other baseline characteristics of the cohort, stratified by quartile of mean perioperative glucose, are displayed in Table 1. The majority of patients were aged in their sixties and slightly more than half were men. African-Americans comprised ~15% of the sample in the lower three glucose quartiles, but were disproportionately represented in the highest quartile, accounting for 25%. Underlying comorbidity before surgery (assessed using the Charlson Comorbidity Index), diabetes severity as indicated by presence of significant proteinuria, and overall severity of illness shortly after surgery (assessed using the APACHE III Prognostic System) were remarkably similar across glucose quartiles. Of patients in the lower three glucose quartiles, ~25% spent >48 h in the surgical intensive care unit after surgery, compared with only 17% of those in the highest quartile. On admission, 41.7% of patients were maintained on standing insulin, 45.1% were maintained on an oral hypoglycemic agent, 11.7% were maintained on diet alone, and 1.5% were maintained on a combined regimen of insulin and an oral hypoglycemic agent.

Postoperative infections

Of the 411 patients, 4 died, 3 of whom suffered infections before their death. The most common complications, in order of decreasing frequency, were leg wound infection (10.9%), urinary tract infections

Table 1—*Baseline characteristics of 411 adults with diabetes who underwent coronary artery surgery by quartile of mean perioperative glucose concentration*

Characteristic	Glucose quartile 1	2	3	4
n	104	102	104	101
Age (years)	64 ± 9	63 ± 10	62 ± 9	62 ± 10
Male (%)	59	51	54	51
Race (%)				
White	84	82	86	72
African-American	16	18	12	25
Other	0	0	2	3
Charlson Comorbidity Index	2.6 ± 1.3	2.5 ± 1.3	2.6 ± 1.2	2.3 ± 1.1
Urine protein ≥2+ (%)	11	8	6	7
APACHE III index	21 ± 9	22 ± 11	21 ± 8	21 ± 7
SICU stay (%)				
0–23 h	39	53	50	50
24–47 h	35	25	24	33
≥48 h	26	22	26	17

Data are *n*, %, or means ± SD. Urine protein results were available for 375 individuals. SICU, surgical intensive care unit.

(6.6%), sternal wound infections (5.6%), and pneumonia (4.6%). Overall, 100 patients developed one or more infections after surgery, corresponding to an overall complication rate of 24.3%. Incidence rates of infectious complications were subsequently calculated after stratification by glucose quartile. These ranged from 20.1 infections per 100 people in quartile 1 to 29.8 per 100 in quartile 3 (Table 2).

Relative odds of infectious complications by glucose quartile

In order to assess the relative odds of infectious complications among patients in the second, third, and fourth quartiles of mean perioperative blood glucose compared with patients in the lowest quartile, a series of multiple logistic regression models were constructed (Table 3). In an unadjusted model (model 1), patients in the third and fourth quartiles appeared to be at increased risk of infection, with relative odds of 1.68 and 1.37, respectively; however, the trend did not reach statistical significance (P = 0.21). To determine the independent association between glycemic control and the risk of infection, a second model (model 2) was constructed that simultaneously adjusted for the effects of age, sex, race, Charlson Comorbidity Index, APACHE III score, and the length of stay in the surgical intensive care unit. Compared with their counterparts in the lowest glucose quartile, the relative odds of infection among individuals in quartiles 2, 3, and 4 were 1.17, 1.86, and 1.72, respectively. In this fully adjusted model, the trend toward an increased risk of infection with higher mean perioperative glucose just reached statistical significance (P = 0.05).

Subsidiary prospective analyses

To minimize the possibility that subclinical infection during the first 36 h following surgery might have accounted for our finding of an increased postoperative infection risk, a subsidiary analysis was performed that excluded individuals who developed infectious complications on postoperative day 2, thereby imposing a 24-h lag between the assessment of exposure and outcome. In addition, this analysis also adjusted for proteinuria, to reduce the possibility that perioperative hyperglycemia was simply a marker for diabetes severity. The results from this analysis were virtually identical to those from the original analyses (Table 3, model 3). A further analysis, limited to surgical wound infections (n = 54), also showed a trend towards increased risk of infection in the higher quartiles compared with the lowest, but this trend did not approach statistical significance because of the restricted number of events. Glycemic control was also characterized by the peak capillary glucose reading in the first 36 h postoperatively. In this analysis, there was no relationship between the peak perioperative glucose reading and the subsequent risk of infectious complications.

Case-control analysis

The decision to characterize perioperative glycemic control using the 6 capillary glucose measurements made before the close of postoperative day 1 was admittedly arbitrary. To determine whether changes in the cutoff time between exposure and outcome assessment would influence the relationship between glycemic control and infection risk, we reanalyzed the data using a retrospective case-control approach. This approach allowed us to compare mean glucose concentrations between cases and controls at daily intervals through postoperative day 7 (Fig. 2). After surgery, both cases and controls had similarly high glucose concentrations of ~260 mg/dl. Over the following 7 days, mean cumulative capillary blood glucose concentration declined gradually in both groups, but this decline was more marked in the controls than in the cases. On postoperative day 1, mean glucose concentration was 5 mg/dl higher in cases than controls; by day 5 the difference grew to 10 mg/dl ($P < 0.05$).

CONCLUSIONS — These data suggest that hyperglycemia is an independent predictor of the short-term risk of infection. Patients with mean glucose concentrations >200 mg/dl within 36 h following surgery were more likely to develop infectious complications than their counterparts who were under better glycemic control. This excess risk was independent of age, sex,

Table 2—*Incidence of any infectious complication by quartile of mean perioperative glucose concentration in 411 adults with diabetes who underwent coronary artery surgery*

Glucose quartile	People at risk (*n*)	Events (*n*)	Incidence rate per 100 patients (95% CI)
1	104	21	20.1 (13.0–29.2)
2	102	22	21.6 (14.0–30.8)
3	104	31	29.8 (21.0–38.6)
4	101	26	25.7 (17.6–35.4)

Table 3—*Relative odds of any infectious complication by quartile of mean perioperative glucose concentration in 411 adults who underwent coronary artery surgery*

Glucose quartile	Model 1	Model 2	Model 3
1	1.00	1.00	1.00
2	1.09 (0.55–2.13)	1.17 (0.57–2.40)	0.94 (0.39–2.26)
3	1.68 (0.89–3.17)	1.86 (0.94–3.68)	1.59 (0.71–3.54)
4	1.37 (0.71–2.64)	1.72 (0.86–3.47)	1.78 (0.79–4.05)
P value	0.21	0.05	0.19

Data are relative odds (95% CI). Model 1 is unadjusted; model 2 is adjusted for age, sex, race, comorbidity index, APACHE score, and surgical intensive care unit stay; model 3 is adjusted for age, sex, race, comorbidity, APACHE III index, surgical intensive care unit stay, and proteinuria, and includes a 24-h lag between exposure and outcome assessment. It is limited to the 375 individuals with available data on proteinuria. *P* value is based on trend test, using mean glucose concentration as a continuous variable.

race, underlying comorbidity on admission, and severity of illness assessed during recovery. Strengths of this study that support these conclusions include a blinded evaluation of outcomes (i.e., data on the exposure—glycemic control—was collected before data on the outcome—infection), substantial data collection on potential confounders, and ascertainment of a wide variety of infectious outcomes.

Nonetheless, five possible limitations of the study deserve mention. First, there were no data on glycemic control (e.g., glycated hemoglobin) before surgery and relatively few data related to diabetic microvascular disease. Therefore, we cannot completely exclude the possibility that perioperative hyperglycemia was a marker for poor long-term glycemic control that conferred risk via preexisting vascular disease. However, the observation that the relationship of perioperative glycemic control to complication risk was independent of age, proteinuria, and comorbidity reduces the likelihood of this possibility. Second, it is possible that subclinical infection within 36 h following surgery led to hyperglycemia. Yet, the results of the lagged analysis suggest that such reverse causality is unlikely. Third, some misclassification bias was likely, in that 36 h may have been too short a time to characterize glycemic control optimally. However, since the case-control analysis indicates that the disparity in glycemic control between cases and controls increased over time, the choice of a cutoff at 36 h appears conservative. Fourth, because this was an observational study in which the level of glycemic control was not randomly assigned, physicians may have chosen tighter control for patients perceived to be at higher risk for infection. In fact, patients with surgical intensive care unit stays >48 h did display better glycemic control. This phenomenon likely biased the results toward the null, producing an underestimate of the true risk associated with hyperglycemia. Finally, the APACHE III predicts in-hospital mortality in critically ill patients but does not include parameters specific to diabetes, such as HbA_{1c}, the presence of albuminuria, or previous history of cardiovascular disease. APACHE III is, however, a well-standardized and accepted system for assessing acute risk in all critically ill patients, regardless of underlying comorbidity.

One possible explanation for the excess risk of infection in diabetic individuals is based on the association of diabetes with micro- and macrovascular disease and their consequences. Vascular disease may disrupt normal nutrient and oxygen delivery to tissues and thereby impair host defenses (2,3). Peripheral neuropathy may allow undetected disruption of the skin barrier, creating a portal of entry for bacteria (3). High post-void residual volumes related to bladder dysfunction increase the likelihood of urinary tract infections. Under this hypothesis, the relationship of hyperglycemia with

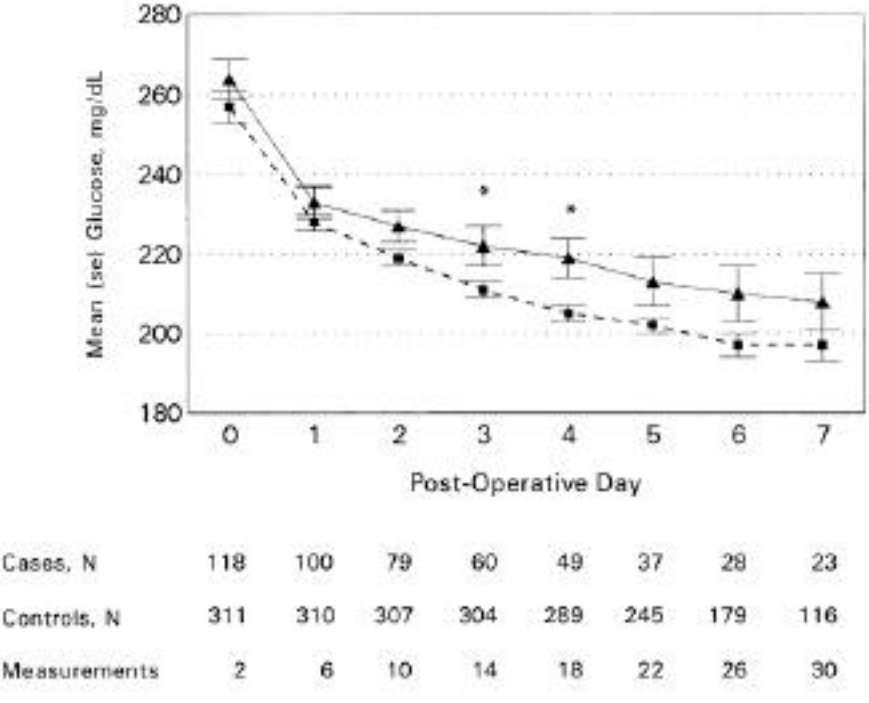

Figure 2—*Cumulative mean capillary glucose concentration in 434 diabetic patients who underwent coronary artery surgery, by postoperative day and infectious complication case-control status. The solid line represents individuals who developed infections (cases); the dotted line represents those who did not (control subjects). The cumulative mean capillary glucose concentration in milligrams per deciliter is shown for cases (▲) and control subjects (■) on each postoperative day. Bars represent 1 SEM. Cumulative means plotted for day* x *correspond to case-control status on day* x + *1 (cases occurring on or before day* x *are censored, as are individuals who died or who were discharged from the hospital), and include all glucose measurements from the day of surgery through 11:59* P.M. *of day* x. **Statistically significant (*P < *0.05, two-tailed) difference in mean cumulative glucose between cases and control subjects. The data table summarizes the number of cases and controls contributing to each mean, as well as the typical number of capillary blood glucose measurements accumulated through the end of the corresponding postoperative day.*

the risk of infection is indirect, mediated by the long-term effect of hyperglycemia on the progression of vascular disease. Therefore, short-term differences in blood glucose concentration should have little or no influence on the risk of bacterial infection.

An alternative explanation is based on the observation that hyperglycemia produces direct short-term impairments of a variety of host defense mechanisms, entirely distinct from its adverse effect on the arterial system. Hyperglycemia may produce high tissue levels of glucose and the formation of edema related to increased vascular permeability, both of which may promote bacterial growth (2,3). High glucose levels in endothelial tissues may alter the redox state of cells so as to mimic the effects of tissue hypoxia, despite normal oxygen tension ("pseudohypoxia") (21). At very high concentrations (>900 mg/dl) glucose binds to the active site of protein C3 in the complement cascade, thereby inhibiting its attachment to the microbial surface and impairing opsonization (9). Finally, diabetic individuals in poor glycemic control have abnormalities in lymphocyte number (2) and function (8).

By far the best-studied short-term consequence of hyperglycemia related to infection is its effect on human neutrophil function, with >100 publications since 1960. This literature was most recently reviewed by Pozzilli and Leslie in 1994 (2). A variety of abnormalities in neutrophil function in diabetic individuals have been documented such as decreased chemotaxis (22,23), decreased phagocytosis (6,7, 24–26), decreased bacterial killing (5–7,27), increased adhesiveness, which may hinder extravasation (22,28), and chronic activation, which may be associated with the overproduction of harmful free radicals (22). The degree of neutrophil dysfunction was proportional to blood glucose concentration in most (5–7,25,26,29–36), but not all (22,27,28,37–39) studies. Six studies evaluated specific glycemic thresholds for neutrophil dysfunction (25,27,29,31,32,40). In these six, the median glycemic threshold was 200 mg/dl, with a range of 130–275 mg/dl.

Although in vitro studies generally favor the notion of a short-term effect of hyperglycemia on infection risk, results from four previous clinical studies are mixed—in fact, three of the four are negative. Hjortrup et al. (12) studied 224 diabetic adults who underwent surgery at a general hospital in Copenhagen from 1975 to 1982. On average, the 54 patients who went on to develop postoperative complications (including pulmonary and vascular events) actually had lower levels of perioperative glycemia than their counterparts who did not. MacKenzie and Charlson (11) studied a similar cohort of 282 diabetic adults who underwent surgery at New York Hospital in 1980. While diabetes-related end-organ disease (e.g., retinopathy, nephropathy, peripheral vascular disease) predicted postoperative complications (n = 42), perioperative glycemic control did not. As in Hjortrup's study, no subgroup analysis confined to infectious outcomes was performed. Finally, in a cohort of 146 diabetic patients who underwent cardiac surgery at William Beaumont Hospital in 1988, Fietsam et al. (13) found higher levels of perioperative glycemia in the 11 who went on to develop infectious complications (mean glucose on postoperative day 2 = 261 mg/dl) compared with their counterparts who suffered cardiopulmonary complications (187 mg/dl) or who averted any complication (221 mg/dl). However, because of the small number of events, these estimates were imprecise and the contrast between them was statistically insignificant. Besides limitations in statistical power, none of these three negative studies accounted for factors such as underlying comorbidity or postoperative severity of illness that might confound the relationship of hyperglycemia to infection risk.

The sole clinical evidence which supports this relationship comes from the study of Zerr et al. (10) published in 1997. They investigated the occurrence of deep wound infections in a cohort of 1,585 individuals with diabetes who underwent cardiac surgery at a general hospital in Portland, Oregon, from 1987 to 1993. There was a strong, graded relationship of wound infection risk (n = 33) with the mean concentration of blood glucose on postoperative day 1, rising from 1.3% among patients with glucose levels in the 100–150 mg/dl range to 6.7% among those with levels in the 250–300 mg/dl range. Although results from a fully adjusted multivariate model were not shown, this relationship was at least independent of two potentially confounding factors—BMI and type of surgery. Unfortunately, this study was limited by confounding related to a major secular trend. In 1991, the cardiac surgery service implemented a new protocol for diabetic patients that tightened perioperative glycemic control significantly. Thus, in this cohort, "tight control" also serves as a proxy for calendar time (e.g., 1993 patients were in tighter control than 1987 patients). In this situation, it is difficult to separate the effects of tight control per se, from other, unrelated improvements in surgical practice which might have occurred in that interval.

Guidelines for the perioperative care of patients with diabetes have recommended levels of glycemic control high enough to avoid hypoglycemia, but low enough to avoid excess catabolism, ketoacidosis, and hyperosmolarity (14,15). In the absence of compelling data from clinical studies, guidelines have had to rely heavily on data from in vitro studies of neutrophil function to set an upper bound on glycemia. Recommended ranges for preprandial glucose levels following surgery include 120–200 mg/dl (14) and 125–180 mg/dl (15) from recent reviews, and 150–200 mg/dl from textbooks of surgery (16) and consultative medicine (17,41).

The main implication of our study is that hyperglycemia, particularly mean blood glucose levels >200–230 mg/dl, is associated with an increased short-term risk of infection following surgery. This result provides empiric clinical support for published recommendations on the perioperative care of individuals with diabetes. Definitive confirmation would require the conduct of a randomized controlled trial of aggressive versus conventional glycemic control for surgical patients with diabetes. The feasibility of such a hospital-based intervention has recently been demonstrated (42). In the meantime, because current practice appears to produce levels of perioperative glycemia >230 mg/dl ~50% of the time, our study should prompt physicians to consider tightening glycemic control for their diabetic patients in the perioperative setting.

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