Insulin Infusion Improves Neutrophil Function in Diabetic Cardiac Surgery Patients

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Diabetic patients are at increased risk of wound infection after major surgery, but the effect of perioperative glucose control on postoperative wound infection rates after surgery is uncertain. We tested the effect of an insulin infusion on perioperative neutrophil function in diabetic patients scheduled for coronary artery bypass surgery. Participants ($n = 26$) were randomly allocated to receive either aggressive insulin therapy (AIT) or standard insulin therapy (SIT) during surgery. Blood was drawn for neutrophil testing before surgery, 1 h after the completion of cardiopulmonary bypass, and on the first postoperative day. Neutrophil phagocytic activity decreased to 75% of baseline activity in the AIT group and to 47% of baseline activity in the SIT group ($P < 0.05$ between groups). No important differences in neutrophil antibody-dependent cell cytotoxicity were found. This study documents a potentially beneficial effect of continuous insulin therapy in diabetic patients who require major surgery. **Implications:** A continuous insulin infusion and glucose control during surgery improves white cell function in diabetic patients and may increase resistance to infection after surgery.

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The infectious complications of cardiac surgery can have devastating clinical consequences. Septic mediastinitis causes severe morbidity and has a high mortality rate. Other infectious complications, such saphenectomy wound infections or nosocomial pneumonia, also add significantly to the morbidity and cost of cardiac surgery.

Patients with diabetes who require coronary artery surgery have an increased susceptibility to perioperative infections (1–3) and a higher rate of serious morbidity (1,2,4,5). Several factors may contribute to an increased complication rate in diabetics, including poor preoperative nutritional status (6), concurrent obesity (4), and preexisting immune deficiencies (7).

Infectious complications in diabetic patients who undergo coronary artery bypass grafting (CABG) are associated with impaired immunity after surgery (8). The mechanism for impaired postoperative immune function in diabetics is unclear and is probably multifactorial (9–11). However, hyperglycemia may play an important role in altering leukocyte function, including the function of polymorphonuclear neutrophils (PMNs) (9–16). There is *in vitro* evidence that control of glucose concentrations improves immune function (9–13,15,16), but the clinical implications of glucose control for patients with diabetes mellitus are unknown. We conducted a clinical study to examine the effect of aggressive insulin therapy on PMN function in diabetic cardiac surgery patients.

Methods

After approval by the Dartmouth-Hitchcock Medical Center Committee for the Protection of Human Subjects, written informed consent was obtained from 26 patients with diabetes scheduled to undergo elective cardiac surgery with cardiopulmonary bypass (CPB). All patients underwent surgery starting at 8:00 AM at the Dartmouth-Hitchcock Medical Center during 1996 and 1997. Exclusion criteria included emergency surgery, conditions known to cause immunosuppression (other than diabetes mellitus), age <18 yr, or inability to provide written informed consent.

Patients were prospectively randomized into one of two treatment groups: standard insulin therapy (SIT group) or aggressive insulin therapy (AIT group). The anesthesia and surgery team was not blinded as to the choice of insulin therapy.

The SIT group patients who were taking insulin were given one half of their usual subcutaneous NPH insulin

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dosage the morning of surgery and started on an infusion of 5% dextrose with 0.45% sodium chloride solution at 50 mL/h. Oral hypoglycemics were not given the morning of surgery. Glucose levels were checked 1 h before surgery and then repeated intraoperatively using an automated device (AccuData™GTS; Boehringer Mannheim Corporation, Indianapolis, IN). IV regular insulin was administered according to the following schedule:

Glucose level (mg%)	Insulin (U)
<200	0
200–250	3
250–300	5
300–350	7
350–400	9
400–450	11

For high glucose levels (>450 mg%), an infusion of insulin was started after an IV bolus of 13 U. The infusion was started at 4 U/h and titrated hourly.

Patients randomized to the AIT group who were taking insulin were given one half of their usual subcutaneous NPH insulin dosage the morning of surgery and started on an infusion of 5% dextrose with 0.45% sodium chloride solution at 50 mL/h. Oral hypoglycemics were not given the morning of surgery. Glucose levels were checked 1 h before surgery, and the patients were started on an insulin infusion according to the following protocol, modified from Zerr et al. (17):

Glucose level (mg%)	Insulin (U/h)
<150	0
150–200	1
201–250	2
>250	3

Further insulin was titrated according to the following protocol (glucose levels were checked every 15–30 min):

Glucose level (mg%)	Action
75–100	Stop insulin, recheck glucose until above 150 mg%, restart with rate 50% of previous rate.
101–150	Decrease rate by 0.5 U/h, or if glucose is 10 mg% lower than last test, decrease rate by 50%.
151–200	Continue same rate.
201–250	If lower than last test, same rate; if higher than last test, increase rate by 0.5 U/h. (If the rate of glucose increase is rapid, increases of 2–6 U/h acceptable).
>250	If lower than last test, same rate; if higher than last test, increase rate by 1 U/h (see above).

If glucose >250 mg% and has not decreased after three successive increases in insulin, then the insulin administration rate doubled.

Glucose levels were checked until stable and until frequent changes in insulin dosage were no longer necessary. Postoperative insulin therapy was not controlled by the study protocol and consisted of an IV infusion of insulin as directed by the protocol of Zerr et al. (17) in all patients in both study groups.

The anesthetic technique included premedication with an H_2-blocker for those patients with a history of gastroesophageal reflux and titrated doses of midazolam (1–5 mg) and fentanyl (50–200 μg). General anesthesia consisted of fentanyl 20–50 μg/kg, midazolam 2–10 mg (or diazepam 5–20 mg), pancuronium 0.1–0.2 mg/kg, and isoflurane 0.2%–1.5% in an oxygen/air mixture. Vasoactive medications and blood product transfusions were administered at the discretion of the anesthesiologist. All patients received prophylactic perioperative antibiotics. Epsilon aminocaproic acid was used for all patients, except for those judged to be at high risk of inadequate hemostasis, for whom aprotinin was used. CPB was conducted at normothermia with a membrane oxygenator. A centrifugal blood pump was used. The pump prime consisted of a mixture of plasmalyte and mannitol with or without 6% hetastarch. Intraoperative red cell scavenging and processing for transfusion was also used. All surgical procedures were performed via a median sternotomy.

Peripheral blood for immunologic studies was drawn through an indwelling arterial catheter immediately before the induction of anesthesia, 1 h after separation from CPB, and at 8:00 AM on the first postoperative day.

PMNs were isolated by density gradient centrifugation of heparinized whole blood layered over Polymorphprep™ per the manufacturer's directions (Gibco BRL, Gaithersburg, MD). Cells were washed once with serum-free RPMI 1640 (Gibco BRL). Red blood cells were lysed with sterile water, followed by suspension reequilibration to 1× phosphate-buffered saline. Cells were washed and resuspended in serum-free RPMI. Suspension concentrations were determined using a model JT Coulter Counter (Beckman Coulter, Inc., Fullerton, CA).

Candida organisms were washed twice in serum-free RPMI 1640 to remove growth medium. *Candida* concentration was determined by a wet mount count. In duplicate, 1×10^6 PMNs, 5×10^6 *Candida*, 50 mL of autologous serum, and a balance of serum-free RPMI to a final volume of 500 μL were added to 1.5 mL of polypropylene Eppendorf tubes. The suspensions were vortexed and incubated with constant agitation for 15 min in a 37°C water bath, then placed on ice for 5 min. A wet-mount slide was made and read for percent phagocytosis of at least 200 PMNs per sample (number of PMNs with ingested yeast/total number

of PMNs counted ×100 = percent phagocytosis). Results were reported as the average of the duplicates.

As previously described (18), chicken red blood cells (cRBCs) were labeled with ^{51}Cr in fetal calf serum (FCS) for 1 h at 37°C and 5% CO_2. After washing twice with 10% FCS/RPMI 1640, cells were adjusted to 0.5×10^6 cells/mL and 1 mL of packed ox red blood cells per milliliter of adjusted cRBCs was added. Rabbit anti-cRBC antibody dilutions were prepared in 10% FCS/RPMI 1640 to achieve final assay concentrations of 0.003 to 6 mg/mL. Isolated PMNs were adjusted to 10×10^6 cells/mL in 10% FCS/RPMI 1640. In triplicate, in a 96-well assay plate, the following were added for the appropriate conditions: for experimental samples, 50 μL of antibody dilutions, 50 μL of PMNs, and 50 μL of cRBCs; for maximal lysis, 100 μL of 2% Triton-X and 50 μL of cRBCs; for spontaneous lysis, 100 μL of media and 50 μL of cRBCs; for antibody control, 50 μL of 6 mg/μL, 50 μL of cRBCs, and 50 μL of media. The plate was centrifuged at 100*g* for 3 min and incubated in 37°C and 5% CO_2 for 4 h. After incubation, 75 μL of supernatant was collected from each well and transferred into 6 × 50 mm borosilicate tubes, sealed with paraffin, and counted on a γ counter for 1 min. Cytotoxicity was determined as follows:

$$\% \text{ cytotoxicity} = 100 \times \frac{\text{mean experimental lysis} - \text{mean spontaneous lysis}}{\text{mean maximal lysis} - \text{mean spontaneous lysis}}$$

Using previously published data (10), we determined that group sizes of 13 patients per study group would give us 84% power to detect a significant (20%) increase in PMN function in the treatment groups after surgery at a 5% level of significance.

Unadjusted comparisons between treatment groups were performed using the Wilcoxon rank sum statistic for continuous variables or by using the χ^2 statistic with continuity correction for dichotomous outcomes. Adjusted comparisons were performed using generalized estimating equations that incorporated the dependent nature of the data (the same patient was observed on multiple occasions), adjusted for baseline differences and modeled for other possible confounders.

Results

From March 1996 to June 1997, 26 diabetic patients were enrolled, of whom 13 were randomized to the AIT group and 13 to the SIT group. Their demographic data are shown in Table 1. There were no important differences between groups with regard to gender, age, height, weight, body mass index, left ventricular ejection fraction (LVEF), or type of diabetes. Patient care characteristics are also shown in Table 1. There were no significant differences with regard to the procedure performed, the duration of CPB, the use of aprotinin, the amount of blood transfused, the temperature at the end of the procedure, or the amount of opioid administered.

Table 1. Patient Characteristics

	AIT	SIT
n	13	13
Age (yr)	64.3 ± 9.3	68.4 ± 7.5
Weight (kg)	82 ± 16	77 ± 13
BMI (kg/m^2)	27.8 ± 3.4	28.7 ± 3.1
Gender (% male)	77	38
LVEF	0.57 ± 0.14	0.59 ± 0.20
IDDM (%)	50	46
Procedure (*n*)		
CABG	10	11
Valve	1	2
CABG/Valve	2	0
Redo (%)	8	8
CPB time (min)	97 ± 43	102 ± 45
Aprotinin (%)	8	23
PRBC (U)	0.7 ± 0.9	1 ± 1.2
Temperature (° C)	36.7 ± 0.5	36.3 ± 0.7
Fentanyl (μg)	1783 ± 735	2113 ± 707

Values are means ±SD unless otherwise indicated.
AIT = aggressive insulin therapy group, SIT = standard insulin therapy group, BMI = body mass index, LVEF = left ventricular ejection fraction, IDDM = insulin-dependent diabetes mellitus, CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, PRBC = packed red blood cells.

The average glucose level for the intraoperative period was significantly reduced in the AIT group ($P = 0.03$) compared with the SIT group (Figure 1). This was confirmed by the regression model, which found the difference in glucose between groups ($P < 0.001$) to be unaffected by type of diabetes mellitus, age, gender, height, or weight of the patient. The percent change in glucose levels from baseline, averaged per 15-min time period in the two groups, is shown in Figure 2. The average baseline glucose level was 172 ± 65 mg% in the AIT group and 152 ± 51 mg% in the SIT group.

A marked reduction in PMN phagocytosis activity occurred 1 h after CPB in the SIT group. The change in neutrophil activity was not as pronounced in the AIT group (Figure 3). The phagocytic activity decreased from 55% at baseline to 41% 1 h after CPB in the AIT group, and from 49% to 23% in the SIT group during the same time periods ($P = 0.025$ for the difference between the two groups 1 h after CPB). The percent decrease from baseline was 25% in the AIT and 54% in the SIT, and the difference between the two groups was significantly different ($P = 0.02$). On the first postoperative morning, phagocytic activity returned to 85% of baseline values in both groups.

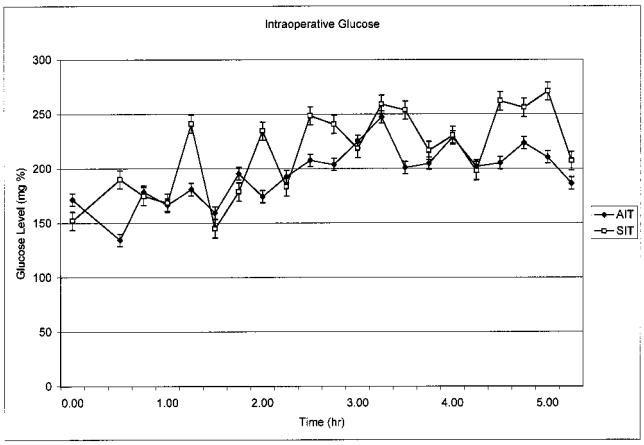

Figure 1. Intraoperative glucose level (± SE). AIT = aggressive insulin therapy, SIT = standard insulin therapy.

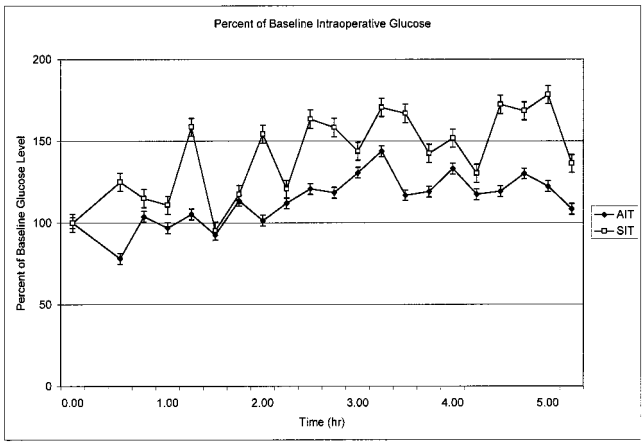

Figure 2. Percent of baseline glucose levels (± SE). AIT = aggressive insulin therapy, SIT = standard insulin therapy. Glucose levels were significantly reduced in the AIT group compared with the SIT group ($P < 0.05$).

The regression model supports the unadjusted analysis. Adjusting for baseline phagocytosis, there was a statistically significant increase in phagocytosis for the treatment group 1 h postoperatively. There was no observed difference at baseline. Age, height, weight, use of aprotinin, CPB time, type of DM, or LVEF were not significant predictors of phagocytosis, nor did they affect the estimate of the observed treatment effect. Although gender was a statistically significant predictor of phagocytosis ($P < 0.041$), it did not influence our estimate of treatment effect.

PMN antibody-dependent cell cytotoxicity (ADCC) activity demonstrated a decrease in both the AIT and SIT groups 1 h after CPB, then a slight increase in both groups 24 h after surgery (Table 2). For both groups, at most antibody concentrations, the change from baseline 1 h after CPB reached statistical significance. The intergroup comparisons showed that, 24 h after surgery, there was a trend toward an increase in activity

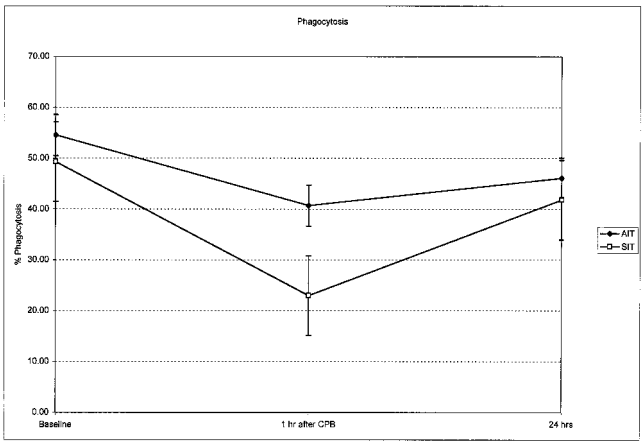

Figure 3. Percent phagocytic activity of peripheral blood polymorphonuclear neutrophils (PMNs) at baseline, 1 h after cardiopulmonary bypass (CPB), and 24 h postoperatively. AIT = aggressive insulin therapy, SIT = standard insulin therapy. One hour after CPB, the difference between phagocytic activity between the AIT group and the SIT group was statistically significant ($P < 0.02$).

Table 2. Changes in ADCC of PMNs During and After Cardiac Surgery

	Antibody concentration (μg/mL)	AIT (%)	SIT (%)
Baseline			
	6	71 ± 10	72 ± 9
	1.5	65 ± 9	65 ± 9
	0.375	51 ± 9	52 ± 18
	0.187	33 ± 10	40 ± 21
	0.094	16 ± 9	18 ± 15
	0.047	9 ± 6	12 ± 11
One hour after CPB			
	6	64 ± 9	69 ± 6
	1.5	57 ± 9	62 ± 12
	0.375	33 ± 8	42 ± 22
	0.187	20 ± 7	29 ± 19
	0.094	10 ± 5	13 ± 12
	0.047	4 ± 3	6 ± 6
Postoperative Day 1			
	6	64 ± 6	68 ± 9
	1.5	56 ± 8	63* ± 10
	0.375	45 ± 6	53 ± 12
	0.187	35 ± 8	45 ± 15
	0.094	21 ± 11	31 ± 16
	0.047	13 ± 10	20 ± 18

Values are mean ±SD.
AIT = aggressive insulin therapy, SIT = standard insulin therapy, CPB = cardiopulmonary bypass, ADCC = antibody-dependent cell cytotoxicity, PMN = polymorphonuclear neutrophil.
* $P = 0.046$.

in the SIT group compared with the AIT group. However, this reached statistical significance only at the high antibody concentration of 1.5 μg/mL ($P = 0.046$).

Although this study was not designed to compare groups with regard to infectious complications, we did observe two major infections (one case of septic mediastinitis and one case of nosocomial pneumonia) and one minor infection (an uncomplicated urinary

tract infection) in the SIT group. There were no infectious complications in the AIT group.

Discussion

The results of this study suggest that aggressive glucose control may improve the nonspecific phagocytic activity of neutrophils from diabetic patients who undergo CABG surgery. In 1971, Mowat and Baum (9) demonstrated that PMNs from diabetic patients showed decreased chemotaxis compared with PMNs from normal subjects. Furthermore, the observed defect in chemotaxis could be corrected by incubating the PMNs with insulin. Subsequently, researchers found that the rate of phagocytosis and bacterial killing by PMNs from patients with poorly controlled diabetes was decreased compared with PMNs from normal subjects (10). With treatment aimed at improving blood glucose control (insulin or oral hypoglycemics), PMN phagocytic activity was restored and bacterial killing improved. More recent investigations demonstrate that the PMN respiratory (oxidative) burst, part of the intracellular pathogen lysis mechanism, is inhibited by increased glucose concentrations *in vitro* (11). When PMNs from nondiabetic subjects were incubated with varying levels of glucose, respiratory burst in response to various stimuli was inhibited in a concentration-dependent fashion. Further investigations confirmed that, when incubated with glucose, PMNs from nondiabetics showed diminished superoxide generation with a marked inhibition of phospholipase D activity (13). This supports the theory that proteins important in the generation of superoxide may be altered by hyperglycemia.

The effect of glucose control on the perioperative immune response in diabetic patients is poorly characterized. Kwoun et al. (19) demonstrated that acute hyperglycemia in rats induced a decrease in respiratory burst of alveolar macrophages (but not peripheral PMNs) while the animals were anesthetized for a standardized surgical procedure. They also observed enhanced phagocytosis by alveolar macrophages. Only one large clinical series has addressed the question of glucose control and wound infections in patients with diabetes after cardiac surgery (17). These investigators instituted a protocol with the goal of maintaining postoperative blood glucose <200 mg% with an insulin infusion in diabetic cardiac surgical patients. In the 5 yr before the institution of this protocol, the rate of infection was 2.4%, whereas in the 3 yr after protocol initiation, the infection rate decreased to 1.5%, a statistically significant difference. During the same time period, the mean glucose level on the first postoperative day decreased from 206 to 172 mg% ($P < 0.005$), a modest difference comparable to that which we observed during surgery. Independent predictors of wound infection included a higher postoperative glucose level and obesity. The authors concluded that improved glucose control through the use of an insulin infusion led to fewer infectious complications in their patients with diabetes.

The main result of this study is improved phagocytic activity in the period immediately after CPB in patients randomized to aggressive glucose control. This is the first randomized trial, with appropriate controls, to demonstrate that impairment in PMN function in diabetics during surgery is at least partially reversible. Consistent with previous *in vitro* and animal studies, we found glucose control only affected nonspecific neutrophil function. Specifically, antibody-dependent function was unaffected by insulin therapy and returned to normal on the first postoperative day.

Glucose levels were only modestly, but significantly, improved in the AIT group compared with the SIT group through the use of an insulin infusion and frequent blood glucose measurements. These findings are consistent with the hypothesis that improved glucose control leads to improved PMN phagocytic function. In addition, there may be other direct or indirect effects of insulin on the immune system, which may account for some or all of the observed differences. It is possible that endocrinological or cytokine-mediated effects of insulin therapy may have a positive impact on PMN phagocytic function.

CPB induces alterations in PMN function, including altered chemotaxis (20), altered leukotriene generation (21), depressed adhesion (22), and depressed phagocytosis (23). Furthermore, anesthesia and the stress response to surgical trauma can also affect PMN function (24). Given the combined effects of CPB, anesthesia, surgical trauma, stress response, and exogenous as well as endogenous catecholamines, detection of immunologic effects from a brief intraoperative insulin infusion suggests a strong independent influence from this intervention.

Several limitations of this study should be acknowledged. First, peripheral blood PMN function is not the end point of greatest concern. Improvements in PMN activity may translate into decreased rates of infection, but documentation of such an effect awaits appropriate clinical trials. Second, we did not stratify patients according to adequacy of chronic glucose control, as might be measured by hemoglobin A_{1C} (HbA_{1c}). In addition, we included patients with noninsulin–dependent diabetes mellitus and patients with insulin-dependent diabetes mellitus, creating a slightly heterogeneous patient population. However, evidence implicates hyperglycemia *per se* as causing impairment of PMN function and not the duration or physiologic etiology for the increased glucose levels (11–16,19). This is supported further by work demonstrating that PMNs from patients with diabetes display improved activity when glucose levels are returned to normal (13). Furthermore, Delamaire et al.

(25) demonstrated that the type of diabetes, the HbA_{1C} level, and the disease duration do not explain depressed chemotaxis and chemiluminescence observed in PMNs from diabetics. Third, the differences in PMN function may be explained by unobserved differences between the two groups, a possibility that exists for all randomized, controlled trials.

In summary, we demonstrated that a protocol-driven IV infusion of insulin during cardiac surgery leads to improved glucose control. Furthermore, the group of patients randomized to receive aggressive control of glucose with the use of an insulin infusion had improved phagocytic function of peripheral blood PMNs immediately after CPB compared with a standard therapy group.

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