Tight Glycemic Control in Diabetic Coronary Artery Bypass Graft Patients Improves Perioperative Outcomes and Decreases Recurrent Ischemic Events

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Background—This study sought to determine whether tight glycemic control with a modified glucose-insulin-potassium (GIK) solution in diabetic coronary artery bypass graft (CABG) patients would improve perioperative outcomes.

Methods and Results—One hundred forty-one diabetic patients undergoing CABG were prospectively randomized to tight glycemic control (serum glucose, 125 to 200 mg/dL) with GIK or standard therapy (serum glucose <250 mg/dL) using intermittent subcutaneous insulin beginning before anesthesia and continuing for 12 hours after surgery. GIK patients had lower serum glucose levels (138±4 versus 260±6 mg/dL; P<0.0001), a lower incidence of atrial fibrillation (16.6% versus 42%; P=0.0017), and a shorter postoperative length of stay (6.5±0.1 versus 9.2±0.3 days; P=0.003). GIK patients also showed a survival advantage over the initial 2 years after surgery (P=0.04) and decreased episodes of recurrent ischemia (5% versus 19%; P=0.01) and developed fewer recurrent wound infections (1% versus 10%, P=0.03).

Conclusions—Tight glycemic control with GIK in diabetic CABG patients improves perioperative outcomes, enhances survival, and decreases the incidence of ischemic events and wound complications. (Circulation. 2004;109:1497-1502.)

Key Words: insulin ♦ diabetes mellitus ♦ ischemia

Patients with diabetes mellitus who undergo CABG surgery have increased perioperative mortality and morbidity, significantly reduced long-term survival, and less freedom from recurrent episodes of angina.1-3 The poorer outcomes in these patients have been attributed to a higher incidence of left ventricular dysfunction, altered endothelial function, more diffuse coronary disease, abnormal fibrinolytic and platelet function, and impaired glucose utilization.4 These risk factors were thought to be irreversible, thus predisposing diabetic CABG patients to less favorable short- and long-term prognoses.

There is now evidence to suggest that achieving tighter glycemic control in diabetic patients during acute coronary syndromes improves survival. In the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study, Malmberg and coworkers5 reduced mortality after an acute myocardial infarction (MI) by 30% with the infusion of a glucose-insulin solution designed to achieve serum glucose levels <200 mg/dL. These favorable effects persisted for a mean of 3.5 years.6 On the basis of the DIGAMI study, we designed a modified glucose-insulin-potassium (GIK) solution that resulted in tighter control of perioperative serum glucose in diabetic CABG patients.7 This study was therefore undertaken to determine whether tight perioperative glycemic control in diabetic CABG patients with a modified GIK solution would optimize myocardial metabolism and improve perioperative outcomes. We also sought to determine whether the early beneficial effects of tight glycemic control would result in improved survival, a decreased incidence of ischemic events, and reduced wound complications.

Methods

Patients with diabetes mellitus undergoing primary or reoperative CABG performed on cardiopulmonary bypass were included in the study. Approval to use GIK solutions in human subjects was obtained from the Boston University Medical Center Institutional Review Board (Protocol E 3270/A65). An informed consent was obtained from each patient enrolled in the study.

Patients were randomly assigned to a GIK or No-GIK group. The GIK group received an infusion through a central line consisting of 500 mL D5 W with 80 U of regular insulin and 40 mEq of KCl infused at 30 mL/h, prepared by a research pharmacist. The GIK was started just before anesthetic induction and continued until cardiopulmonary bypass was instituted. It was then discontinued and restarted after the aorta was unclamped and continued for 12 hours after arrival in the Intensive Care Unit (ICU). Blood glucose and K+ were monitored every hour. Adjustments in the rate of the GIK infusion were made on the basis of the scale shown in Table 1.
Patients in the No-GIK group received D5W infused at 30 mL/h. Blood glucose and K⁺ were also monitored every hour, and the scale shown in Table 2 was used to administer subcutaneous insulin.

After the 18-hour study period, patients resumed their preoperative diabetic regimens (oral agents or insulin) titrated to keep blood glucose <200 mg/dL.

All vessels with at least 50% stenoses were bypassed, and at least 1 internal mammary artery was used in each patient. Myocardial protection consisted of multidose infusions of antegrade, cold (4°C) blood (hematocrit 20%), potassium (28 mEq/L), cardioplegia supplemented with mild systemic (35°C) and topical (cold saline lavage at 4°C) hypothermia.

Measurements of heart rate, arterial blood pressure, pulmonary capillary wedge pressure, cardiac output, cardiac index, and systemic vascular resistance were monitored continuously from the time of anesthesia induction to 18 hours after arrival in the ICU. Serum glucose and potassium levels were measured before the infusion of GIK and every hour until patients had been in the ICU for 18 hours. Serum lactates and free fatty acids were measured before induction, immediately before initiating cardiopulmonary bypass, and at 0, 6, 12, and 18 hours after admission to the ICU.

Inotropic agents were used to maintain a cardiac index ≥2.0 L/min per m² and a systolic blood pressure ≥90 mm Hg after afterload, preload, and heart rate were maximized. An inotropic score was used to identify the number of inotropic agents used, the dosage, and length of administration. The score ranged from 0 to 5, where 0=no inotropic agents or dopamine ≥2 µg/kg for ≤24 hours; 1=dopamine ≥2 µg/kg for ≥24 hours; 2=2 inotropic agents; 3=the use of epinephrine; 4=3 inotropic agents; and 5=inotropic support >24 hours.

ECGs were obtained before CABG, immediately on arrival in the ICU, and on postoperative days 1, 2, 5, and 7. The myocardial fraction of creatine kinase and lactate dehydrogenase isoenzyme levels were measured immediately after surgery and at 6 and 24 hours postoperatively. A perioperative MI was diagnosed either by the appearance of new ECG changes (Q waves, ST-segment elevation ≥1 mm, loss of R wave in the precordial leads) or by the elevation of creatine kinase MB levels ≥50 IU in the immediate 24-hour period after surgery. All patients were placed on telemetry during their postoperative hospital stay, and the incidence of atrial fibrillation was recorded. β-Blockers were instituted before surgery and continued throughout the postoperative period in all patients with a heart rate ≥60 bpm and a systolic blood pressure ≥95 mm Hg.

All patients were weighed the evening before surgery and at 5:00 AM the day after surgery to determine the postoperative weight gain in pounds. The time spent on the ventilator was recorded in hours from the time of admission to the ICU to the time of extubation. All patients were placed on standardized “fast-track” protocols. Length of stay in the ICU was defined as time from ICU arrival to transfer to the floor or step-down unit. Before transfer, patients had to be extubated with stable vital signs and without any inotropic support. Hospital length of stay was defined as the time from the date of surgery to the day of discharge. Criteria for discharge included a stable cardiac rhythm, temperature <99°F, a well-healed incision, and oxygen saturations >90% on room air or supplemental oxygen ≤2 L. Patient follow-up was obtained directly by telephone to assess angina class. Hospital records were used to document catheterizations, the incidence of ischemic episodes, recurrent infections, and mortality. Recurrent ischemic events were described as episodes of angina with ECG changes or documented MIs with enzyme and ECG changes.

The 2 study groups (GIK, No-GIK) were compared on continuous variables via 2-sample t tests and on categorical variables via χ² tests of homogeneity and Fisher’s exact tests. Repeated measures on continuous dependent variables by study group were assessed in repeated measures ANOVAs with independent groups. Time to death was compared between groups by Kaplan-Meier estimation and tested via a log-rank test. Results of the repeated-measures ANOVA are displayed in figures as mean±SEM. Results were deemed significant when probability values were <0.05. Analyses were performed using SAS, version 8.2, software.

### Results

One hundred forty-one patients were enrolled into the study and completed the protocol without any study-related complications. The preoperative patient profiles are summarized in Table 3. There was no difference in age, sex, ejection fraction, urgency of surgery, or the type of diabetes between the groups.

There was no difference in the incidence of vessels with ≥50% stenoses (3.24±0.08 GIK versus 3.16±0.07 No-GIK...
Figure 1. Serum glucose. Glycemic control is achieved in GIK-treated patients, even after solution has been terminated at 18 hours. CPB indicates cardiopulmonary bypass.

Figure 2. Serum lactates. Serum lactates remain lower during infusion of GIK and increase at 18 hours once GIK is terminated. CPB indicates cardiopulmonary bypass.

Figure 3. Free fatty acids. Serum free fatty acids are lower over first 6 hours in ICU but begin to rise as infusion of GIK decreases. CPB indicates cardiopulmonary bypass.

Table 4. Postoperative Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>GIK (n=72)</th>
<th>No GIK (n=69)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day mortality</td>
<td>0</td>
<td>0</td>
<td>0.99</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>0 (0)</td>
<td>2 (2.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>Pacing, n (%)</td>
<td>10 (13.8)</td>
<td>27 (39)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>12 (16.6)</td>
<td>29 (42)</td>
<td>0.002</td>
</tr>
<tr>
<td>Infections (pneumonia and wound, n (%))</td>
<td>0 (0)</td>
<td>9 (13)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time on ventilators, h</td>
<td>6.9±0.3</td>
<td>10.7±0.6</td>
<td>0.0002</td>
</tr>
<tr>
<td>Maximum weight gain, lb</td>
<td>6.8±0.5</td>
<td>13.3±0.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Inotropic score</td>
<td>1.18±0.06</td>
<td>2.16±0.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Intensive care unit stay, h</td>
<td>17.3±1.0</td>
<td>32.8±2.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative hospital stay, d</td>
<td>6.5±0.1</td>
<td>9.2±0.3</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Mean serum potassium levels were constant in both groups throughout the perioperative period (4.54±0.05 mEq/L GIK versus 4.47±0.04 mEq/L No-GIK; P=0.43). The changes in serum glucose are shown in Figure 1. Both groups had similar glucose levels at the time of anesthetic induction (180.4±6.9 mg/dL GIK versus 179.0±3.8 mg/dL No-GIK; P=0.86). However, after the initiation of GIK therapy, GIK-treated patients achieved significantly better glycemic control immediately before cardiopulmonary bypass (169.2±4.9 mg/dL GIK versus 209.2±5.3 mg/dL No-GIK; P<0.0001) and after 12 hours in the ICU (134.3±3.7 mg/dL GIK versus 266.8±6.3 mg/dL No-GIK; P<0.0001). This trend persisted at 18 hours even though GIK was no longer being infused (170.6±5.3 mg/dL GIK versus 257.1±6.0 mg/dL No-GIK; P<0.0001). The favorable affects of tighter glycemic control were reflected in serum lactates (Figure 2). Serum lactate levels were significantly lower at 6 hours (1.75±0.14 mmol/L GIK versus 2.33±0.31 mmol/L No-GIK; P=0.04) and 12 hours (1.36±0.11 mmol/L GIK versus 2.24±0.19 mmol/L No-GIK; P<0.001) during GIK infusion but tended to increase at 18 hours after the GIK infusion was terminated (1.65±0.11 mmol/L GIK versus 1.81±0.12 mmol/L No-GIK; P=0.39). Similarly, free fatty acid levels were significantly lower in GIK-treated patients after 6 hours (0.33±0.03 mEq/L GIK versus 0.57±0.05 mEq/L No-GIK; P<0.001) and began to increase toward the conclusion of the GIK infusion at 12 and 18 hours (Figure 3).

The postoperative results are shown in Table 4. There were no 30-day mortalities in either group. GIK-treated patients had significantly higher cardiac indices (Figure 4) even after the infusion was discontinued at 18 hours (2.91±0.06 L/min per m² GIK versus 2.43±0.06 L/min per m² No-GIK; P<0.0001) and less need for pacing and inotropic support. Patients treated with GIK gained less weight (6.8±0.05 lb GIK versus 13.3±0.90 lb No-GIK; P<0.0001), spent less time on the ventilator (6.9±0.3 hours GIK versus 10.7±0.6 hours No-GIK; P=0.0002), and had a lower incidence of atrial fibrillation (16.6% versus 42% No-GIK; P=0.0017). Better glycemic control also resulted in a lower incidence of pneumonia and wound infections (0% GIK versus 13% No-GIK; P=0.010). This all contributed to shorter postoperative hospital stays (6.5±0.1 days GIK versus 9.2±0.3 days No-GIK; P=0.003).

Table 5 summarizes the follow-up data obtained over the 5-year study period. Follow-up data were available in 60 of 72 (83.3%) GIK and 60 of 69 (86.9%) No-GIK patients. There was no difference in the preoperative profiles or length of time from surgery in the patients lost to follow-up between the groups. Kaplan-Meier curves (Figure 5) showed a survival advantage for GIK-treated patients during the initial 2 years after surgery (Table 5, P=0.04). One GIK patient died of intractable congestive heart failure; 6 No-GIK patients
died, 5 of cardiac-related causes and 1 of a cerebrovascular accident. GIK-treated patients developed fewer recurrent wound infections involving the leg and sternum (1% GIK versus 10% No-GIK; \( P < 0.03 \)), had decreased episodes of recurrent ischemia (5% GIK versus 19% No-GIK; \( P = 0.01 \)), and maintained a lower angina class (angina class=0: 95% GIK versus 80% No-GIK; \( P = 0.03 \)). Four patients were recatheterized in each group. One patient in the GIK group and one in the No-GIK group underwent percutaneous interventions.

**Discussion**

To develop new strategies to improve outcomes in diabetic CABG patients, it is important to understand the mechanisms responsible for impaired function in the diabetic ischemic myocardium. During periods of ischemia, glucose is the preferred metabolic substrate for the myocardium. However, glucose oxidation in the diabetic heart is markedly impaired, not only as a result of impaired glucose transport into the myocytes but also by the reduced rate of phosphorylation of glucose within the cell. Concentrations of free fatty acids are increased, which are detrimental to the ischemic myocardium because they increase oxygen consumption, inhibit glucose utilization, decrease contractility, predispose to arrhythmias, and increase free radical accumulation.\(^8\) Insulin resistance, which is known to occur during cardiopulmonary bypass, also contributes to increased concentrations of free fatty acids and decreased myocardial uptake of glucose.\(^9\)

In addition to alterations in myocardial metabolism, diabetic CABG patients may also incur further ischemic damage because of the augmented inflammatory response and increased production of superoxide radicals, which leads to endothelial dysfunction. Diabetic patients with coronary disease have increased levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor, which stimulate the synthesis of acute-phase proteins such as C-reactive protein.\(^10,11\) This increased inflammatory response can contribute to the postoperative capillary leak syndrome, which results in increased lung water accumulation and altered autonomic tone. As a result, these patients have increased fluid accumulation and require longer periods of ventilatory support. Diabetic patients also have impaired endothelial function. Hyperglycemia depletes NADPH and increases the synthesis of diacylglycerol, both of which result in decreased synthesis of endothelial nitric oxidase synthase, a potent vasodilator.\(^12\) This results in increased production of endothelin-1, a potent vasoconstrictor, which has been shown to increase cell necrosis after periods of ischemic injury.\(^13\) Bioassays from internal mammary artery and saphenous vein grafts taken from diabetic CABG patients show decreased NO activity and increased production of superoxide and NADPH oxidase.\(^14\) This altered endothelial function during CABG may result in postoperative ischemic necrosis and may contribute to decreased long-term survival and recurrent ischemic events. Patients with diabetes also have impaired platelet function characterized by increased levels of plasminogen activator inhibitor-1 and adhesion molecules.\(^15,16\) This enhances platelet adhesiveness and hyperaggregability and
predisposes to coronary thrombosis, which may ultimately affect long-term vein graft patency.

Intravenous infusions of insulin after CABG surgery have been shown to decrease levels of free fatty acids and increase myocardial uptake of glucose. Insulin added to cardioplegic solutions in CABG patients enhances aerobic metabolism on reperfusion and improves left ventricular stroke work index. Exogenous insulin also decreases oxidative stress and the inflammatory response. Low-dose infusions of insulin (2 IU/h) in obese patients significantly decreased levels of reactive oxygen species, adhesion molecules, and C-reactive protein within 2 hours. Insulin may also prevent coronary thrombosis by 2 mechanisms. It upwardly regulates the l-arginine–NO pathway, which improves endothelial function, and it decreases serum levels of plasminogen activator inhibitor-1.

Several studies have shown that hyperglycemia is associated with adverse outcomes during acute coronary syndromes. Wahab and colleagues studied the effects of increased blood glucose in 1664 patients admitted with an acute MI. Patients with a blood glucose >198 mg/dL had higher in-hospital and 1-year mortalities independent of whether or not a history of diabetes was present. Norhammar and coworkers also noted that elevated serum glucose levels in acute MI patients, regardless of a known history of diabetes, was a risk factor for reinfarction, congestive heart failure, and future cardiovascular events. Similar results were noted by Iwakura and colleagues, who demonstrated that hyperglycemia in association with acute coronary syndromes predicted larger infarcts, decreased contractility, and less reperfusion by contrast echocardiography. Furnary and coworkers, in a retrospective, nonrandomized study of diabetic patients undergoing CABG over a 14-year period, found that patients receiving a continuous insulin drip in the postoperative period had tighter control of serum glucose levels than patients managed with intermittent subcutaneous insulin injections, and, as a result, there was a significant decrease in perioperative mortality in the patients treated with a continuous insulin infusion (2.5% versus 5.3%; P<0.0001). The decrease in mortality was primarily because of a decrease in the incidence of cardiac-related deaths.

Although our study provides no mechanisms for the beneficial effects of GIK on enhanced survival, we hypothesize that the potential of GIK for improving endothelial function, decreasing vascular inflammation, and reducing thrombogenicity contributed to improved early graft patency and enhanced viability of myocardial cells in areas of ischemia. This might explain the improved survival, which is largely accounted for by the decreased mortality in GIK patients within 2 years after surgery. A similar early survival benefit was seen in the DIGAMI trial in a group of diabetic patients receiving insulin during an acute MI. The improved endothelial function, suppressed inflammatory response, and decreased thrombogenicity afforded by GIK in diabetic patients during reperfusion of acutely ischemic myocardium may be especially protective of areas with jeopardized, dysfunctional myocardium. This modification of the reperfusion injury by GIK may also explain why it appears to be especially effective during revascularization of acutely ischemic myocardium in both diabetic and nondiabetic patients.

Our study has several limitations. The results are derived from a single center. Clinicians were not blinded to the treatment groups, introducing the possibility of bias, although it is unlikely that this affected the incidence of atrial fibrillation, wound infections, mortality, or recurrent ischemic events. The non-GIK patients were allowed to reach higher glucose levels before insulin was administered, raising the possibility that this group was undertreated. However, this protocol represented the standard of care of perioperative glucose control in many cardiac centers and did not result in an increase in 30-day mortality in these patients. Our study suggests that 30-day operative mortality alone may not be the best predictor of long-term outcomes in diabetic CABG patients. As in any study involving outcomes in CABG patients, long-term ischemic events are not as clearly defined as immediate postoperative events. For this reason, we not only included ischemic episodes but also documented finite end points such as mortality, infections, recatheterizations, and angina class.

This study has shown that maintaining serum glucose ≤200 mg/dL using a modified GIK solution in diabetic patients decreases perioperative morbidity, enhances survival, and diminishes recurrent ischemic events. Can superior results be obtained if serum glucose levels are further lowered? A recent study in critically ill patients receiving mechanical ventilation treated with insulin to maintain serum glucose values ≤110 mg/dL had significantly decreased morbidity and less multiorgan failure and were less likely to require prolonged ventilation. Is insulin the key ingredient in improving clinical outcomes, or is substrate enhancement with glucose equally important? A recent study in rats involving an isolated preparation of 30 minutes of ischemia and 4 hours of reperfusion suggests that it is insulin, and not the glucose or potassium, that confers myocardial protection by enhancing NO synthase through P13-kinase–AKT pathways. However, ischemic hearts on cardiopulmonary bypass may benefit from substrate enhancement with glucose. Are the favorable effects of GIK related to enhanced ATP production or a decrease in inflammation and oxidative stress, resulting in improved endothelial function? Future studies will address these issues as we strive to develop new solutions of glucose, insulin, and potassium in an attempt to further reduce perioperative morbidity and enhance long-term survival while providing new insight into the mechanisms responsible for these beneficial effects.

Acknowledgment
This study was supported by a clinical research award from the American Diabetes Association.

References


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Circulation. 2004;109:1497-1502; originally published online March 8, 2004;
doi: 10.1161/01.CIR.0000121747.71054.79
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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