We attempted to develop an insulin administration protocol that maintains normoglycemia in patients undergoing cardiac surgery and to study the effects of intraoperative blood glucose management on serum levels of creatine phosphokinase isoenzyme BB (CK-BB) and S-100 protein. Twenty nondiabetic patients were randomly allocated to receive either “tight control” of blood glucose with a standardized IV insulin infusion intraoperatively (Group TC) or “no control” of blood glucose intraoperatively (Group NC). Perioperative serum levels of glucose, CK-BB, and S-100 protein were determined in all patients. Group TC patients received 90.0 ± 49.2 units of insulin, whereas Group NC patients received none. Despite insulin, both Group TC (P = 0.00026) and Group NC (P = 0.00003) experienced similar significant increases in blood glucose levels during hypothermic cardiopulmonary bypass. However, mean blood glucose level upon intensive care unit arrival was significantly decreased in Group TC, compared with Group NC (84.7 ± 41.0 mg/dL, range 32–137 mg/dL vs 201.4 ± 67.5 mg/dL, range 82–277 mg/dL, respectively; P = 0.0002). Forty percent of Group TC patients required treatment for postoperative hypoglycemia (blood glucose level < 60 mg/dL). Substantial interindividual variability existed in regard to insulin resistance. The investigation was terminated after we realized that normoglycemia was unattainable with the study protocol and that postoperative hypoglycemia was unpredictable. All patients in both groups experienced similar significant increases in postoperative serum levels of CK-BB and S-100 protein. These results indicate that “tight control” of intraoperative blood glucose in nondiabetic patients undergoing cardiac surgery was unattainable with the study protocol and may initiate postoperative hypoglycemia. Implications: The appropriate intraoperative management of hyperglycemia and whether it adversely affects neurologic outcome in patients after cardiac surgery remains controversial. This investigation reveals that attempting to maintain normoglycemia in this setting with insulin may initiate postoperative hypoglycemia.

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examinations is controversial for a number of reasons (8). Biochemical markers (measured in cerebrospinal fluid and/or serum) have been used to assess subtle neurologic injury in patients after cardiac surgery in a manner less subject to measurement vagaries (9). The most promising biochemical markers for assessing subtle neurologic injury in patients after cardiac surgery are the creatine phosphokinase isoenzyme BB (CK-BB) and S-100 protein. In this prospective, randomized, clinical study, we attempted to develop an insulin administration protocol that maintains normoglycemia in patients undergoing cardiac surgery and study the effects of intraoperative blood glucose management on serum levels of CK-BB and S-100 protein.

Methods

After institutional review board approval and informed consent, 20 nondiabetic patients scheduled for elective coronary artery bypass grafting (CABG) participated in the study. Patients receiving preoperative insulin and/or oral hypoglycemics were not studied. Patients requiring preoperative IV inotropic drugs, intraaortic balloon support, or mechanical ventilation were excluded from participation in the study. Any patient exhibiting significant pulmonary, endocrine, metabolic, or neurologic pathology was also excluded.

All patients had their cardiac medications continued through the morning of surgery. Prior to arrival to the operating room, each patient was randomized to receive either “tight control” of blood glucose intraoperatively (Group TC) or “no control” of blood glucose intraoperatively (Group NC). Group TC patients had an IV insulin (Humulin® R regular insulin, Eli Lilly and Company, Indianapolis, IN) infusion initiated during induction of anesthesia that was continued until sternal closure at the end of surgery (see the Appendix for insulin administration protocol). In all patients, arterial blood samples were obtained prior to induction of anesthesia (baseline) and every 20 min after induction of anesthesia for determination of blood glucose levels. The last intraoperative blood glucose level was obtained during sternal closure at the end of surgery when the insulin infusion was stopped. Group NC patients were not administered insulin to control intraoperative blood glucose levels. All patients in both groups received only normal saline for perioperative IV infusion.

The intraoperative anesthetic technique was the same for all patients and consisted of IV fentanyl (20 µg/kg), midazolam (14 mg, total), and vecuronium. All of the fentanyl was administered prior to sternotomy. Regarding midazolam, 10 mg was administered prior to sternotomy and 4 mg administered during rewarming. If required, inhaled isoflurane and/or IV nitroglycerin were used for blood pressure control before initiation of CPB. Hypothermic CPB (to a lowest temperature of 28°C) with a membrane oxygenator and crystalloid prime (2.0 L of lactated Ringer’s solution, 50 mEq of sodium bicarbonate, and 12.5 g of mannitol) was used in all patients. Nonpulsatile flows were maintained between 2.4–2.8 L · min⁻¹ · m⁻² and, if needed, isoflurane was used by the perfusionist to maintain perfusion pressure in the range of 50–70 mm Hg. Alpha-stat blood gas management was used in all patients. Separation from CPB was facilitated with IV inotropic and/or vasoactive drugs at the discretion of the anesthesiologist managing the case. Intraoperative surgical care was not altered in any way in either group.

To assess the effects of intraoperative blood glucose management on changes in serum CK-BB and S-100 protein, six arterial blood samples were obtained from each patient: immediately prior to induction of anesthesia (baseline); immediately after separation from CPB; and 2, 4, 6, and 24 h after separation from CPB. Blood samples were centrifuged within 15 min, and the serum was stored at −20°C until analysis. CK-BB concentrations were measured with the use of a commercially available two-site monoclonal antibody technique as described by Rossi et al. (10). S-100 protein concentrations were measured with the use of a commercially available two-site monoclonal immunoradioactive assay as described by Westaby et al. (11).

After completion of CABG, patients were transferred to the intensive care unit. Postoperative care was standardized for all patients, and extubation was accomplished at the earliest clinically appropriate time. Postoperative complications and treatments were recorded daily for all patients until hospital discharge.

Fisher’s exact test was applied to categorical data. Student’s t-test (two-tailed) was used to test the difference between means in the two groups. A P value of <0.05 was considered statistically significant, and P values are reported only when significance was found. Results are expressed as the mean ± 1 sd unless otherwise indicated.

Results

Of the 20 nondiabetic patients enrolled and participating in the study, 10 were randomly allocated to Group TC and 10 to Group NC. Demographic and clinical characteristics of patients and intraoperative data are presented in Tables 1 and 2, respectively.

In Group TC patients, despite administration of IV insulin (increased infusion rate, supplementary injections), we were unable to attain normoglycemia with the study protocol. Group TC patients received 90.0 ± 49.2 units of insulin (range 40–161 units), whereas Group NC patients received none. Table 3 presents perioperative blood glucose levels for both groups. Although both Group TC (P = 0.00026) and Group NC (P = 0.00003)
experienced significant increases in blood glucose levels during CPB (when compared with baseline), there was no difference between groups. However, mean blood glucose level at sternal closure and upon intensive care unit arrival was significantly decreased in Group TC (Table 3).

Table 4 presents individual data for the 10 Group TC patients. Four patients (40%) required treatment for postoperative hypoglycemia (blood glucose level <60 mg/dL).

Perioperative CK-BB and S-100 protein levels are presented in Table 5. Both Group TC (P = 0.005) and Group NC (P = 0.006) experienced significant increases in serum levels of CK-BB (comparing baseline with peak). Likewise, both Group TC (P = 0.009) and Group NC (P = 0.001) experienced significant increases in serum levels of S-100 protein (comparing baseline with peak). However, there were no differences between groups.

All patients in both groups had an uneventful intraoperative course. Postoperatively, two patients in Group TC and four patients in Group NC developed new-onset atrial fibrillation. No patient in either group experienced perioperative myocardial infarction. The only clinical neurologic morbidity encountered postoperatively occurred in one Group NC patient who developed transient left arm and left leg weakness with aphasia on the second postoperative day that was completely resolved by the fourth postoperative day. This patient had a history of seizures and was taking phenytoin preoperatively. All patients in both groups were eventually discharged from the hospital. Mean postoperative discharge day in Group TC patients (5.5 ± 2.3 days, range 4–10 days) was similar to Group NC patients (6.5 ± 2.0 days, range 3–9 days).
patients after cardiac surgery (9). Both of our groups experienced significant postoperative increases in serum levels of CK-BB and S-100 protein. However, there was no difference between groups, perhaps because of similar intraoperative blood glucose levels and/or small sample size.

Although a large body of convincing evidence indicates that glucose worsens outcome from focal and global cerebral ischemia (1), investigations using a battery of neuropsychologic examinations have failed to show a correlation between intraoperative blood glucose levels and neurologic outcome (1,2). One investigation demonstrated that perioperative hyperglycemia actually benefited patients undergoing cardiac surgery by decreasing perioperative fluid requirements and decreasing postoperative fluid retention (6). However, other investigations indicate that hyperglycemia during profound hypothermic circulatory arrest (10,12) or during normothermic CPB (13) may contribute to neurologic dysfunction. Although not extensively studied, likely causes of hyperglycemia during and after CPB include decreased insulin secretion and peripheral glucose use (hypothermia, pancreatic hypoperfusion) and/or increased activity of insulin antagonists (glucagon, epinephrine, norepinephrine, growth hormone, and cortisol) (14).

We were unable to attain normoglycemia in Group TC patients despite administration of IV insulin (increased infusion rate, supplementary injections) with a standardized protocol. Both groups experienced similar significant increases in blood glucose levels during CPB. This lack of difference between groups may have been a result of the small number of patients studied and/or the large interindividual variability among patients. However, patients receiving insulin had significantly decreased blood glucose levels postoperatively, and 40% required treatment for hypoglycemia. Although the cause(s) of hyperglycemia during and after CPB remains

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**Table 5. Perioperative CK-BB and S-100 Protein Levels**

<table>
<thead>
<tr>
<th></th>
<th>Group TC (n = 10)</th>
<th>Group NC (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CK-BB (ng/mL)</td>
<td>3.1 ± 3.7</td>
<td>1.7 ± 2.6</td>
</tr>
<tr>
<td>Peak CK-BB (ng/mL)</td>
<td>10.7 ± 9.0</td>
<td>10.8 ± 8.6</td>
</tr>
<tr>
<td>Baseline S-100 protein (µg/L)</td>
<td>2.1 ± 2.5</td>
<td>2.9 ± 4.0</td>
</tr>
<tr>
<td>Peak S-100 protein (µg/L)</td>
<td>7.1 ± 5.5</td>
<td>9.7 ± 6.3</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± 1 SD. No differences were observed between groups.

TC = “tight control,” NC = “no control,” CK-BB = creatine phosphokinase isoenzyme BB.

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**Discussion**

This investigation revealed that “tight control” of intraoperative blood glucose was not attainable in these nondiabetic patients undergoing elective CABG and hypothermic CPB with our protocol. Furthermore, 40% of patients receiving insulin required treatment for postoperative hypoglycemia (blood glucose level <60 mg/dL) and insulin administration did not affect postoperative serum levels of CK-BB and S-100 protein. These results indicate that attempting to maintain normoglycemia in this setting with insulin may initiate postoperative hypoglycemia.

The appropriate intraoperative management of hyperglycemia and whether or not it adversely affects neurologic outcome in patients after cardiac surgery remains controversial (3–7). Part of the reason for this controversy is that postoperative neurologic dysfunction is difficult to define and assess (8). Biochemical markers (measured in cerebrospinal fluid and/or serum) can be used to assess subtle neurologic injury in patients after cardiac surgery in a manner less subject to measurement vagaries (9). Although less brain-specific than first expected, CK-BB remains the most extensively studied marker in cardiac surgery, and its presence in serum strongly suggests cerebral damage (9). Although the presence of S-100 protein in serum after CPB may represent either cerebral injury or increased blood-brain barrier permeability, studies indicate that it may be a highly sensitive and specific biochemical marker of neurologic injury in patients after cardiac surgery (9). Both of our groups experienced significant postoperative increases in serum levels of CK-BB and S-100 protein. However, there was no difference between groups, perhaps because of similar intraoperative blood glucose levels and/or small sample size.

Although a large body of convincing evidence indicates that glucose worsens outcome from focal and global cerebral ischemia (1), investigations using a battery of neuropsychologic examinations have failed to show a correlation between intraoperative blood glucose levels and neurologic outcome (1,2). One investigation demonstrated that perioperative hyperglycemia actually benefited patients undergoing cardiac surgery by decreasing perioperative fluid requirements and decreasing postoperative fluid retention (6). However, other investigations indicate that hyperglycemia during profound hypothermic circulatory arrest (10,12) or during normothermic CPB (13) may contribute to neurologic dysfunction. Although not extensively studied, likely causes of hyperglycemia during and after CPB include decreased insulin secretion and peripheral glucose use (hypothermia, pancreatic hypoperfusion) and/or increased activity of insulin antagonists (glucagon, epinephrine, norepinephrine, growth hormone, and cortisol) (14).

We were unable to attain normoglycemia in Group TC patients despite administration of IV insulin (increased infusion rate, supplementary injections) with a standardized protocol. Both groups experienced similar significant increases in blood glucose levels during CPB. This lack of difference between groups may have been a result of the small number of patients studied and/or the large interindividual variability among patients. However, patients receiving insulin had significantly decreased blood glucose levels postoperatively, and 40% required treatment for hypoglycemia. Although the cause(s) of hyperglycemia during and after CPB remains
to be elucidated (14), this investigation suggests that insulin resistance and temperature (not decreased insulin secretion) likely play major roles.

Despite aggressive administration of insulin with our protocol (up to 161 units), normoglycemia was unattainable during hypothermic CPB, and hypoglycemia occurred after CPB (normothermia). Furthermore, after review of individual patient data in Table 4, it is apparent that there is substantial interindividual variability in insulin resistance and in predicting which patients will develop postoperative hypoglycemia. For example, Patient 7 experienced a peak CPB blood glucose level of 496 mg/dL, despite receiving 160 units of insulin, and did not become hypoglycemic postoperatively. On the other hand, Patient 10 required only 40 units of insulin to maintain a peak CPB blood glucose level of 178 mg/dL, yet did become hypoglycemic postoperatively. After review of the initial 20 patients enrolled in this investigation and realizing that normoglycemia was unattainable with our protocol and that postoperative hypoglycemia was unpredictable, the investigation was terminated.

In conclusion, this investigation revealed that “tight control” of intraoperative blood glucose was not attainable in nondiabetic patients undergoing elective CABG and hypothermic CPB with our protocol. Furthermore, 40% of patients receiving insulin required treatment for postoperative hypoglycemia (blood glucose level <60 mg/dL) and insulin administration did not affect postoperative serum levels of CK-BB and S-100 protein. These results indicate that attempting to maintain normoglycemia in this setting with insulin may initiate postoperative hypoglycemia.

Appendix 1. “Tight Control” Group Insulin Administration Protocol

Initiate regular insulin 2 units/hr infusion (0.5 units/mL in normal saline) during induction of anesthesia.

<table>
<thead>
<tr>
<th>If blood glucose</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 mg/dL</td>
<td>Administer 12.5 g of dextrose IVP Stop infusion</td>
</tr>
<tr>
<td>50–100 mg/dL</td>
<td>Stop infusion</td>
</tr>
<tr>
<td>100–150 mg/dL</td>
<td>Maintain current infusion rate</td>
</tr>
<tr>
<td>150–200 mg/dL</td>
<td>10 units of regular insulin IVP Increase infusion by 6 units/h</td>
</tr>
<tr>
<td>200–250 mg/dL</td>
<td>15 units of regular insulin IVP Increase infusion by 8 units/h</td>
</tr>
<tr>
<td>250–300 mg/dL</td>
<td>20 units of regular insulin IVP Increase infusion by 10 units/h</td>
</tr>
<tr>
<td>&gt;300 mg/dL</td>
<td>25 units of regular insulin IVP Increase infusion by 10 units/h</td>
</tr>
</tbody>
</table>

When blood glucose levels decrease, there is a decrease in insulin infusion to the rate at which it was previously at the newly decreased blood glucose level. IVP = IV push (IV bolus).

References