Glucose Homeostasis*
Comparison between Hypothermic and Normothermic Cardiopulmonary Bypass

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Study objective: Disturbance in blood glucose homeostasis during cardiac surgery may cause visceral and metabolic alterations. Hypothermic CPB induces glucose and hormonal changes. As normothermic CPB is used at some institutions, a comparison of blood glucose and plasma hormones between hypothermic and normothermic CPB was performed.

Design: Prospective nonrandomized study.

Setting: University cardiac center.

Patients: Twenty-two nondiabetic adults undergoing elective coronary bypass and/or valvular surgery.

Interventions: Group 1 (n = 12) underwent hypothermic CPB (25°C) and group 2 (n = 10) normothermic CPB (37°C). In both groups nonpulsatile CPB was achieved with a membrane oxygenator and dextrose-free crystalloid priming. Dextrose was not administered during surgery but was infused postoperatively (125 mg/kg/h).

Measurements and results: Eight blood samples were drawn during the period of arrival in the operating room (control) to the third postoperative hour. During hypothermic CPB in group 1, blood glucose level increased to 154 ± 20 mg/dl (mean ± SD) associated with a decrease in plasma insulin and an increase in epinephrine, despite a decrease in cortisol and growth hormone. During rewarming, the blood glucose value continued to increase (to 197 ± 35 mg/dl) associated with an increase in glucagon, growth hormone and catecholamines, despite a 374 percent increase in insulin. During CPB in group 2, insulin, glucagon, cortisol and catecholamines were significantly higher than during hypothermic CPB so that the blood glucose level was not significantly different between the two groups during CPB.

Blood glucose value was higher in group 1 than in group 2 at closure of the chest (205 ± 30 vs 175 ± 19 mg/dl, respectively, p < 0.02) and at the third postoperative hour (371 ± 30 vs 221 ± 51 mg/dl, p < 0.01). In both groups, however, the postoperative increase in blood glucose was accompanied by a similar increase in insulin, cortisol and catecholamines but glucagon was lower after hypothermic CPB.

Conclusions: Hyperglycemia occurred perioperatively in cardiac surgery with dextrose-free priming both during hypothermic and normothermic CPB but normothermic CPB resulted in a slow and steady increase in both glucose and insulin concentrations without the major perturbations that occurred with hypothermic CPB. Postoperatively, higher blood glucose was observed in the hypothermic CPB group.

(Chest 1992; 102:106-11)

N ormothermic cardiopulmonary bypass is used in some centers.1-3 In a previous study, Kuntschen et al4 found that normothermic CPB resulted in higher blood glucose levels than hypothermic CPB. To our knowledge, this is the only study comparing glucose homeostasis during normothermic vs hypothermic CPB. As the two groups of patients studied by these authors were operated on under different conditions (different countries, types of anesthesia and methods of cardiac protection) we performed a prospective study comparing glucose homeostasis in patients operated on with the same protocol except CPB temperature.

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Methods

Patients

After obtaining approval of the ethics committee of our Institution (December 27, 1987) and informed patient's consent, 22 adults underwent CABG or valvular replacement (Table 1). Patients with diabetes mellitus, clonidine treatment or requiring emergency surgery were excluded. Due to the nyctohemeral endocrine variations, all operations started at 8:00 AM.

Anesthesia

All patients were anesthetized by the same physician (J.J.L.) to ensure a consistent anesthetic approach. All cardiac medications were continued until the day before surgery. Orally administered diazepam (0.35 mg/kg) was given as premedication and induction of anesthesia consisted of fentanyl (50 µg/kg), diazepam (0.25 mg/ kg) and pancuronium (0.1 mg/kg). Anesthesia was maintained with increments of fentanyl and diazepam. Artificial ventilation was provided by a Servo ventilator A (Siemens-Elema, Germany) (n = 10/ min, VT = 10 ml/kg, oxygen = 100 percent). Radial artery and pulmonary artery Swan-Ganz catheters were inserted prior to induction with the patient under local anesthesia. Central temperature were monitored through rectal and pulmonary artery catheter probes. Ringer's lactated solution and vasodilators (nitroglycerin,
sodium nitroprusside) were administered as needed. No dextrose was administered throughout surgery except 820 mg per blood unit.

Cardiopulmonary bypass

After injection of heparin (300 U/kg), the venous cannula was inserted into the right atrium and the arterial cannula into the root of the ascending aorta. The patients were allocated to one of two groups according to the surgeon's routine: group 1 (n = 12) underwent hypothermic CPB (Injection temperature = 25°C) and group 2 (n = 10) underwent normothermic CPB (Injection temperature = 37°C).

A CML membrane oxygenator (Cobe, Arvada, Colo) and a nonpulsatile pump (Sarns, Ann Arbor, Mich) were used. As Stephens et al have shown that Ringer's lactated solution priming does not modify blood glucose, the priming consisted of Ringer's lactated solution (1,500 ml), sodium bicarbonate 1.4 percent (300 ml) and heparin (5,000 U). Saint Thomas' Hospital crystalloid cardioplegic solution without glucose was injected at 4°C into the aortic root immediately after aortic cross-clamping and every 20 min thereafter until unclamping. As is standard practice in our institution, mean arterial pressure was maintained between 50 and 80 mm Hg by adjusting perfusion index and use of nitroglycerin. Vasopressor agents were not used in these patients during CPB.

A heating mattress (38°C) was used continuously, except during cooling, in group 1. In this group re-warming did not begin before 30 min of CPB had passed, and the patients were re-warmed at 37°C (pulmonary artery temperature).

Reversal of heparin was accomplished with protamine sulfate, 4 mg/kg; aprotinin, 2,000,000 protease inhibitory units (Iniprol, Choay, Paris, France), was administered simultaneously.

Postoperative Period

After transfer to the ICU the patients were ventilated overnight with the same ventilator adjusted according to blood gas levels. Sedation consisted of subcutaneously administered morphine chloride (0.1 mg/kg). A 10 g/L dextrose infusion was started at the arrival in the ICU at the rate of 1.25 ml/kg/h.

Protocol

Pulmonary artery temperatures were measured and blood samples were drawn at the following interval times: control, 15 min after insertion of catheters (A); 5 min after tracheal intubation, before incision (B); 15 min (C) and 30 min (D) after starting CPB; at termination of CPB when cardiac mechanical activity had resumed (E); immediately (F), 1 h (G) and 3 h (H) after closure of the chest.

Arterial blood was sampled at these interval times for glucose level, (Technicon RA-100, Domont, France), acid-base status, blood gas values (alpha-stat, not corrected for patient's temperature), hematocrit and plasma hormone concentrations. Blood lactate levels were measured at the onset and at the completion of CPB.

After centrifugation, the plasma was frozen at −40°C for later assay of the following hormones: epinephrine and norepinephrine, by HPLC with electrochemical detection after extraction on alumina; insulin, cortisol and GH, by RIA according to methods previously described, and glucagon by RIA (Kit Serono-Biodata, Rome, Italy). The normal values in adults at 8:00 AM are as follows: glucose—65 to 100 mg/dl; epinephrine—39 to 51 pg/ml; norepinephrine—195 to 295 pg/ml; insulin —< 30 µU/ml; cortisol—350 to 650 pmol/ml; GH—< 5 ng/ml; glucagon—25 to 100 pg/ml. Blood glucose and hormones were not assayed when patients received sympathomimetic drugs.

During the 4 h following surgery, episodes of shivering were recorded by a nurse unaware of the patient's group.

Statistical Analysis

Parametric data were analyzed by two-way analysis of variance and paired t test for intragroup comparison with levels of significance adjusted to control for multiplicity (Bonferroni) and unpaired t test for intergroup comparisons. Nonparametric data were analyzed by Wilcoxon's test. Differences were significant when probability was less than 0.05. The results were expressed as mean ± SD in the text and the tables and as mean ± SEM in the figures.

Results

The groups were not significantly different for anthropometric data, preoperative treatment and type of surgery (Table 1). However, CPB and aortic clamping durations were significantly longer in group 1 because of the duration of cooling and re-warming. No significant differences in the amount of injected anesthetics and muscle relaxant were found. The group 1 patients were administered 1.5 ± 1.4 (range: 0 to 4) blood units and the group 2 patients 1.6 ± 1.5 (range: 0 to 4) blood units during the study duration.

No patient died during the study period. Sympathomimetic drugs were administered in four group 1 patients after CPB (epinephrine: one, dopamine: three) and in two group 2 patients (epinephrine: one, dobutamine: two). The patient in group 1 to whom epinephrine was administered required intra-aortic balloon pumping. In group 1, nitroglycerin was administered intravenously to five patients and sodium nitroprusside was administered to two patients during the study period. Nitroglycerin was administered to two group 2 patients. No patient received sympatho-

Table 1—Demographic and Surgical Data (Mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 12)</th>
<th>Group 2 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60 ± 9</td>
<td>55 ± 14</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>9/3</td>
<td>8/2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 ± 14</td>
<td>74 ± 14</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 9</td>
<td>168 ± 7</td>
</tr>
<tr>
<td>Preoperative treatment</td>
<td></td>
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</tr>
<tr>
<td>Digoxin</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nitrate</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Duration of aortic cross-clamping (min)</td>
<td>53 ± 16</td>
<td>40 ± 13*</td>
</tr>
<tr>
<td>Minimum rectal temperature (°C)</td>
<td>30.4 ± 1.2</td>
<td>35.9 ± 0.6*</td>
</tr>
<tr>
<td>Hematocrit before induction</td>
<td>0.42 ± 0.04</td>
<td>0.44 ± 0.05</td>
</tr>
<tr>
<td>Minimum hematocrit during CPB</td>
<td>0.25 ± 0.05</td>
<td>0.28 ± 0.03</td>
</tr>
</tbody>
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*Group 1 vs group 2 (p<0.05).

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mimetic drugs before or during CPB.

In Group 1, four patients presented with a total of 16 shivering episodes during the 4-h postoperative period vs no patient in group 1 (p<0.05).

Two group 1 patients presented with ECG and enzymatic evidence of perioperative MI vs one group 2 patient. This last patient died 13 h after the end of surgery because of intractable arrhythmia and low cardiac output. No severe arrhythmia occurred in the other patients.

Pulmonary artery temperature was similar in the two groups before and after the induction of anesthesia (Fig 1), while it decreased to 25.6±3.2°C in group 1 and 34.3±2.8°C in group 2 (intergroup difference: p<0.001) 15 min after starting CPB and increased to 36.6±0.7°C and 36.1±0.7°C (p>0.05), respectively, at the end of CPB. After the end of surgery, pulmonary artery temperature continued to increase to 37.3±0.7°C in group 2 and was significantly higher than in group 1 (Fig 1).

**Metabolic Data**

Blood gas levels and arterial pH were within physiologic values in all patients without intergroup difference except arterial pH at the end of CPB (7.47±0.06 in group 1, 7.41±0.05 in group 2; p<0.02). At the beginning of CPB, blood lactate level was 4.29±0.46 mmol/L in group 1 and 4.84±0.46 mmol/L in group 2 (p<0.05), and 3.5±0.39 and 4.09±0.45 mmol/L, respectively, at the termination of CPB (p>0.05).

**Blood Glucose**

Blood glucose and plasma hormone concentrations were similar in the two groups before and after induction of anesthesia. Before induction of anesthesia, the patients were slightly hyperglycemic (Fig 1). Blood glucose levels did not change after induction of anesthesia, even though they increased but not significantly in group 1 (+8 percent) and significantly in group 2 (+28 percent) 15 min after starting CPB. This rise was significant in the two groups 30 min after starting CPB (+15 and +39 percent, respectively) and at the end of CPB (+46 and +48 percent, respectively). At the end of surgery and before administration of dextrose, blood glucose levels were 19 percent higher in group 1 than in group 2 (p<0.02).

Postoperatively, after administration of dextrose 125 mg/kg over 1 h, blood glucose increased additionally by 18 and 22 percent, respectively, and reached similar values in group 1 and group 2 (244±47 and 213±46 mg/dl, respectively). However, after administration of dextrose, 375 mg/kg over 3 h, blood glucose increased more in group 1 than in group 2 and reached 271±30 mg/dl and 221±51 mg/dl, respectively (p<0.01). The lowest blood glucose concentration was 108 mg/dl and was found before induction of anesthesia.

![Figure 1. Pulmonary artery temperature, blood glucose, plasma insulin and glucagon concentrations in group 1 (open circles, hypothermic CPB) and in group 2 (normothermic CPB). Values are mean±SEM. Key to symbols: asterisk, different from control; + different from group 1 (p<0.05). C, onset of cooling in group 1; R, onset of rewarming in group 1; D, onset of dextrose infusion in both groups. See text for interval times.](image)
Insulin

In group 1, the plasma insulin concentration decreased by 44 and 60 percent 15 and 30 min, respectively, after starting hypothermic CPB (Fig 1). During rewarming the insulin level increased dramatically (+374 percent). At the end of surgery and at the first postoperative hour, the insulin level returned to control values and presented a second peak at the third postoperative hour. In group 2, no significant change occurred throughout the study period.

Hyperglycemic Hormones

Plasma glucagon concentration did not change significantly throughout the study period in either group (Fig 1). However, a slight increase during CPB in group 2 and a slight decrease during hypothermic CPB in group 1 led to significantly greater values in group 2. In group 1, rewarming was accompanied by an increase in plasma glucagon so that glucagon was similar in the two groups at the completion of CPB. Subsequently, in group 1 glucagon decreased to less than group 2 levels \( p < 0.02 \) at the first postoperative hour.

Plasma cortisol concentration decreased not significantly after induction (Fig 2). In group 1, cortisol further decreased 15 min after starting CPB, then increased continuously throughout the study period. In group 2, a similar evolution was observed but with higher values than in group 1 \( p < 0.05 \) at 15 and 30 min of CPB.

Plasma GH concentration slightly decreased after induction (Fig 2). In group 1, plasma GH further decreased at the beginning of CPB and remained under control levels throughout surgery. In group 2, no significant change occurred with CPB. No intergroup difference was observed.

Plasma epinephrine concentration was almost unchanged by induction of anesthesia (Fig 2). However, these values significantly increased during CPB in the two groups but to a greater extent in group 2. After a slight decline at the end of CPB, epinephrine increased again postoperatively. The evolution of plasma norepinephrine levels was similar to epinephrine.

DISCUSSION

Hyperglycemia may enhance the effects of ischemia, especially in the brain. During cardiac surgery with patients in a state of deep hypothermia, postoperative plasma creatine kinase BB concentrations correlated with blood glucose during reperfusion. In a previous study, Kuntschen et al have shown that blood glucose increased during normothermic but not during hypothermic CPB in the absence of dextrose in the priming solution. By contrast, Mescheryakov et al and Rogers et al observed hyperglycemia during hypothermic CPB with a similar priming.

In the present study, blood glucose was slightly increased before induction of anesthesia, possibly because of elevated plasma GH and catecholamine concentrations due to stress. Blood glucose increased...
both during hypothermic and normothermic CPB. This increase occurred earlier, however, during normothermic CPB than during hypothermic CPB. Before rewarming, blood glucose was lower in hypothermic CPB, but this difference did not reach statistical significance. Although Yokota et al\textsuperscript{15} observed a decrease in the disappearance rate of glucose from the blood during hypothermic CPB, normothermic CPB seemed to be accompanied by a greater decrease in this rate or more likely by a greater glucose production.

By contrast, hyperglycemia was greater after hypothermic CPB at closure of the chest and postoperatively. Hypothermia inhibits hepatic glucose production\textsuperscript{4,14,15} during CPB so that a greater glycogen reserve can be subsequently transformed into glucose after CPB. The residual moderate postoperative hypothermia may also limit glucose utilization although more shivering episodes were observed in this group.

A low plasma insulin concentration has been shown previously during hypothermic CPB\textsuperscript{4,14,15} although Mescheryakov et al\textsuperscript{15} found an increase in plasma insulin. Our data agree with the former authors’ findings. Experimentally an exposure to cold inhibits insulin secretion.\textsuperscript{16} Catecholamines substantially inhibit insulin release through alpha-adrenergic stimulation.\textsuperscript{17} However, in the present study, this explanation is unlikely, since plasma catecholamines and insulin levels were both higher during normothermic CPB than during hyperthermic CPB. Yokota et al\textsuperscript{15} suggested that the suppression of insulin secretion during CPB resulted from a direct inhibitory action of heparin; since in the present study insulin levels decreased selectively during hypothermic but not normothermic CPB, this role of heparin is unlikely.

During rewarming, plasma insulin increased two-fold over preoperative values. Similar findings were reported by Baum et al\textsuperscript{18} This rebound could be due to a hypersecretion of insulin after a reduced release during hypothermia. The concomitant increase in glycemia is explained by the action of hyperglycemic hormones, particularly glucagon which increased simultaneously and has a rapid effect.

At the third postoperative hour, plasma insulin increased by 127 percent over initial values after hypothermic CPB. Because no significant change was observed after normothermic CPB, it could be suggested that hypothermic CPB induces insulin resistance. This may explain the parallel changes in blood glucose and insulin levels during and after hypothermic CPB.

As in the present study, Kuntschen et al\textsuperscript{4} observed no change in plasma glucagon levels during hypothermic CPB and higher concentrations during normothermic CPB. In addition, a glucagon injection did not increase blood glucose during hypothermic CPB.\textsuperscript{4} In our hypothermic group, rewarming elicited glucagon secretion so that plasma concentrations were transiently similar in the two groups at the end of CPB. After hypothermic CPB, glucagon levels were lower than in the normothermic group. Similar findings were observed by Kuntschen et al.\textsuperscript{4} Lower central temperature or a higher blood glucose level after hypothermic CPB may explain this difference. Moreover, it appears that glucagon is not responsible for the greater hyperglycemia observed after hypothermic CPB.

As reported previously,\textsuperscript{4} plasma cortisol concentrations were lower during hypothermic CPB than during normothermic CPB. This result was similar to that of other studies using different anesthetic agents\textsuperscript{19,20} in that plasma cortisol decreased 15 min after starting hypothermic CPB which was most likely because of hemodilution in the face of unchanged secretion. By contrast, cortisol secretion increased during normothermic CPB. After rewarming, cortisol was higher than in the normothermic group in the study of Kuntschen et al\textsuperscript{4} but the difference was not significant in the present study.

In previous studies GH increased before and during normothermic\textsuperscript{3} and hypothermic CPB.\textsuperscript{4,21} In group 1, GH decreased significantly after induction of anesthesia and 15 min after starting hypothermic CPB, then slightly increased at 30 min of CPB. A parallel trend was observed in group 2 but the changes were not significant. Similar results were found by Sebel et al\textsuperscript{22} with hypothermic CPB. Yokota et al\textsuperscript{15} observed decreased plasma GH levels during hypothermic CPB but GH peaks preceded and followed CPB. Differences in anesthetic and perfusion techniques may account for these differences.

In the present study, epinephrine and norepinephrine levels did not increase before CPB, probably due to high-dose fentanyl anesthesia.\textsuperscript{18} During and after CPB, these catecholamines increased in both groups. However, normothermic CPB was accompanied by higher levels than during hypothermic CPB. This difference was not observed in a previous study,\textsuperscript{4} possibly because a lower fentanyl dose was used. Our data are in agreement with Chernow et al\textsuperscript{23} who showed that anesthetized baboons during non-CPB hypothermia over 33°C presented with increased catecholamines, but that catecholamines declined between 31° and 29°C. A similar evolution was observed during hypothermic CPB.\textsuperscript{23}

During rewarming after hypothermic CPB, a 28 percent increase in blood glucose was accompanied by a 374 percent increase in insulin level. This suggests an insulin resistance with an insulin/blood glucose ratio of 10.2 vs 5.1 in the normothermic group. It may be partly explained by concomitant increases in norepinephrine, glucagon and cortisol levels by 20, 58 and 34 percent, respectively. A fivefold reduction in
glucose utilization also suggested an insulin resistance in a previous study.13

The study by Kuntschen et al4 also compared two groups of patients undergoing either hypothermic or normothermic CPB with bubble oxygenators. The patients undergoing hypothermic CPB had slightly greater body dimensions and probably a different diet (Switzerland vs south of France). At induction of anesthesia, they were administered fentanyl, 12.5 μg/kg (vs 2.5 μg/kg), and then nitrous oxide and enflurane. Cardiac arrest was obtained without cardioplegia (vs cold cardioplegic solution). By contrast, the present study used membrane oxygenators and a different anesthesia with higher doses of fentanyl but no anesthetic gases. Our study confirms most of the results of Kuntschen et al4 suggesting that anesthesia and the type of oxygenator have less influence on glucose metabolism than the CPB temperature.

In conclusion, during hypothermic and normothermic CPB, blood glucose increases substantially partly due to hormonal and metabolic changes. Hypothermic CPB is accompanied by lower hormone levels (insulin, glucagon, cortisol, catecholamines) than normothermic CPB. Rewarming is accompanied by increased glucose, insulin, glucagon, cortisol and norepinephrine levels, and by an increase in insulin/blood glucose ratio to a value twice as high as in normothermic CPB, suggesting a greater insulin resistance. Similarly, after completion of hypothermic CPB, higher blood glucose concentrations are observed despite a substantial increase in plasma insulin. Eventually the normothermic CPB resulted in a slow and steady increase in blood glucose with no significant change in insulin level, as opposed to the major perturbations that occurred with hypothermic CPB. Finally, it is suggested that more exogenous insulin should be administered after hypothermic CPB than after normothermic CPB in order to avoid hyperglycemia.

ACKNOWLEDGMENTS: The authors gratefully acknowledge the assistance of physicians J. F. Chassignolle, M.D.; P Y. Carry, M.D.; G. Sassolas, M.D.; Y. Khalifallah, M.D.; C. Blakeley, M.D.; C. Sims, M.D.; and S. Estanove, M.D.; as well as of perfusionists L. Phuon and J. Callot and the secretarial assistance of Ms. S. Vaisaire and Ms. V. Valero.

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