

# Timely Bolus Insulin for Glucose Control during Cardiopulmonary Bypass

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**Abstract:** Hyperglycemia during cardiopulmonary bypass (CPB) with glucose containing cardioplegia is common; normoglycemia is difficult to maintain and failure to do so may result in worse outcomes. The purpose of this quality improvement initiative was to show that a simple timely insulin bolus is more effective for glucose control during CPB with glucose containing cardioplegia than conventional (not standardized) glucose management in historical case-matched controls. A single bolus of insulin (.2 international units per kilogram; iu/kg) was administered, at the time of aortic cannulation, to 211 consecutive patients undergoing cardiac surgery with CPB and glucose containing cardioplegia. A further .1 iu/kg bolus of insulin was given for blood glucose (BG) measurements greater than 10.0 mmol/L (180 mg/dL) during CPB. The control group of 211 historical case-matched patients had glucose management according to anesthesiologist preference

(insulin as a bolus, bolus plus infusion, infusion only, or no insulin). The frequency of hyperglycemia (BG > 11.0 mmol/L; 198 mg/dL) during CPB was significantly less in the study group (22; 10.5%) than in the control group (117; 55.5%) ( $p < .0001$ ). Hyperglycemia in the first 6 hours in the intensive care unit was also significantly less frequent in the study group (5; 2.4%) than in the control group (14; 6.6%) ( $p = .03$ ). Severe hypoglycemia (BG < 2.8 mmol/L; 50.4 mg/dL) occurred in one patient (.47%) in the timely bolus insulin group and five patients (2.3%) in the control group ( $p = .09$ ). The timely bolus insulin method is more efficacious, but equally safe, in preventing hyperglycemia during CPB with glucose containing cardioplegia, compared with conventional (not standardized) insulin treatment in historical case-matched controls. **Keywords:** glucose control, intra-operative, cardiac surgery, insulin treatment. *JECT. 2012;44:34–38*

Hyperglycemia during cardiopulmonary bypass (CPB) is common (1). Maintaining normoglycemia during CPB is difficult, and failure to achieve normoglycemia despite insulin therapy, is common in our unit (in 2006 an audit of 180 cardiac cases found a 17% incidence of glucose >11.0 mmol/L for >60 minutes, unpublished data). In our department the management of hyperglycemia has traditionally been ad hoc according to the individual anesthesiologist's preference.

As a quality improvement effort, we developed a simple technique to potentially control blood glucose (BG) and avoid hypoglycemia during CPB. Using a bolus of insulin shortly before the initiation of CPB and cardioplegia had

been anecdotally successful in our department. Here, we compare the effectiveness and safety of a simple timely bolus dose of insulin to conventional (not standardized) methods of glucose control already in use in our unit.

Hyperglycemia that is commonly seen during CPB is due to a combination of exogenous glucose administration and the relative insulin resistance that develops in response to the stress of surgery and CPB (2–10). Current literature in support of intraoperative glucose control is limited. The only prospective study of intraoperative glucose control in cardiac surgery shows no difference in outcomes between patients treated with insulin infusions to maintain BG between 4.4 and 5.5 mmol/L (80–100 mg/dL) and conventional treatment to maintain BG less than 11.1 mmol/L (200 mg/dL) (11). On the other hand, several retrospective studies have shown improved outcomes with tight intraoperative glucose control with respect to infections, cognitive function, and mortality (12–17). Despite the paucity of strong evidence, it is still common practice in many cardiac surgical units to treat or try and prevent

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intraoperative hyperglycemia. The potential benefit of avoiding hyperglycemia with aggressive insulin therapy has to be weighed against the risk of causing hypoglycemia, particularly during the postoperative period. Severe hypoglycemia (blood glucose concentration  $<2.22$  mmol/L or  $<40$  mg/dL) has a reported incidence of 1.2–7.1% (18–21), while the incidence of mild hypoglycemia (blood glucose concentration  $<3.33$  mmol/L or  $<60$  mg/dL) is as high as 40% (22).

Several successful regimens for the maintenance of normoglycemia during CPB have been published. The hyperinsulinemic-normoglycemic clamp technique, advocated by Sato et al. has been shown to be effective (23), and reproducible (24). However, this technique, like other successful sliding scale methods (25), remains labor intensive with the need for syringe drivers, extra infusion pumps, and the help of dedicated research or nursing staff.

We sought to develop a simple technique that would be effective in controlling blood glucose during and after CPB, while avoiding hypoglycemia.

## MATERIALS AND METHODS

Approval was obtained from the Regional Ethics Committee (Institutional Review Board) to perform a study of timely bolus insulin (TBI) compared with historical case-matched controls in cardiac surgery patients with CPB and glucose containing cardioplegia. The TBI protocol consisted of a bolus dose of short acting insulin (Actrapid<sup>®</sup>, Novo Nordisk Pharmaceuticals, Bagsvaerd, Denmark), .2 IU/kg, at the time of aortic cannulation. A second dose of short acting insulin (.1 IU/kg) was given if a subsequent BG greater than 10 mmol/L (180 mg/dL) occurred during CPB. Five out of 15 cardiac anesthesiologists (“study anesthesiologists”) were selected to administer the protocol.

Inclusion criteria included undergoing cardiac surgery with CPB utilizing standard (glucose-enriched) cardioplegia with anesthetic managed by one of the study anesthesiologists. Standard cardioplegia consisted of a 4:1 ratio of blood combined with “Buckberg” cardioplegia solution, containing 4.1% dextrose in the base solution. Cardioplegia was administered by the perfusionist immediately following aortic cross clamping and every 20 minutes thereafter until release of the aortic cross clamp.

Exclusion criteria included undergoing off-pump coronary artery bypass graft surgery, on-pump coronary artery bypass graft surgery utilizing intermittent cross-clamp/fibrillation, and CPB utilizing non-standard cardioplegia. Two hundred and eleven consecutive patients meeting inclusion criteria received TBI between September 2008 and August 2009.

The historical control group consisted of randomly case-matched patients undergoing cardiac surgery with CPB and standard cardioplegia in the 12-month period prior to the start of the prospective audit. The same exclusion criteria were applied as for the treatment group. Controls were matched based on gender, presence of diabetes, age, and surgical procedure. Glucose management in the control group was according to anesthesiologist preference and included no insulin, bolus insulin, insulin infusion, and bolus plus infusion, representing the non standard approach to glucose management in our department before the quality improvement effort to standardize management. Anesthesia, CPB, and surgical technique remained unchanged in the period of the study and control.

CPB was conducted according to institutional protocol using a Stockert S3 roller pump (Sorin Group, Deutschland GmbH, Munich, Germany), a D905 Avant or D903 EOS membrane oxygenator with hard-shell venous reservoir (Sorin Group, Mirandola, Italy), an AL6 38  $\mu$ m arterial line filter (Pall Corp, Portsmouth, UK), and SmarxT<sup>™</sup> Tubing (Sorin Group USA Inc., Arvada, CO). The circuit was primed with Plasmalyte 148 (Baxter, Auckland, New Zealand), 22.5 g mannitol, 10,000 IU heparin, 500 mL of Voluven 6% (Fresenius Kabi, New Zealand Limited, Auckland, New Zealand), and 1 g cephazolin to a volume of 1650 or 1200 mL. Non-pulsatile blood flow rates of 2.0–3.0 L/min<sup>-1</sup>m<sup>2</sup> and alpha-stat pH management were used with mean arterial blood pressure targeted at 50–80 mmHg. Myocardial protection was achieved using cold 4:1 Buckberg blood cardioplegia (Biomed Ltd., Auckland, New Zealand) with warm reperfusion according to surgeon preference. Mild to moderate hypothermia (32–34°C) was used with blood outlet temperature during rewarming restricted to less than 37°C.

Whole BG was measured every 20–30 minutes during CPB, every 30–60 minutes in the operating room following CPB, and for 6 hours in the Intensive Care Unit (ICU), according to routine practice. Information on demographics, surgical procedure, glucose concentrations, insulin therapy, and the conduct of CPB were obtained from the anesthesia and perfusion records, laboratory reports, ICU charts, and surgical notes. All data were collected by one of two research assistants.

Hyperglycemia was defined as BG greater than 11.0 mmol/L (198 mg/dL). Hypoglycemia was defined as BG of 2.8–3.49 mmol/L (50.4–62.8 mg/dL). Severe hypoglycemia was defined as BG less than 2.8 mmol/L (50.4 mg/dL). The incidences of hyperglycemia, hypoglycemia, and severe hypoglycemia were documented during three periods: during CPB, following CPB but while the patient was still in the operating room, and during the first 6 hours in ICU.

Categorical data are presented as frequencies and percentages (%). Continuous data are presented as mean

**Table 1.** Demographic data.

	Treatment Group (TBI) <i>n</i> = 211	Case-Matched Controls <i>n</i> = 211	<i>p</i> -Value
Male (%)	159 (75)	159 (75)	1.0
Age (years) (mean ± SD)	62.8 (13.1)	62.7 (13.3)	.93
Diabetes (%)	54 (26)	55 (26)	.91
Simple procedure* (%)	156 (74)	168 (80)	.17
Complex procedure† (%)	54 (26)	42 (20)	.16
Cardioplegia total volume (mL) (mean ± SD)	3564 (1702)	3012 (1108)	<.0001
CPB time (min) (mean ± SD)	129 (50)	119 (49)	.04
Aortic cross clamp time (min) (mean ± SD)	91.8 (40.4)	84.7 (36.8)	.0608

\*Isolated coronary artery bypass grafting or a single valve replacement/repair.

†Double valve, combination valve + coronary artery bypass graft/Maze/other procedure, ascending aortic surgery with or without deep hypothermic arrest, and cardiac transplant.

± standard deviation (SD). The difference of two independent proportions tests was used to determine significant differences in frequencies of the demographic variables and rate of occurrences of hyperglycemia and hypoglycemia between the two groups. For continuous data, the differences between the treatment and control group were assessed by using two-tailed *t* test. All *p*-values resulted from two-sided tests, and a *p*-value of less than .05 was considered statistically significant. Statistical analyses were performed with SAS software version 9.1.3 (SAS Institute, Cary, NC).

## RESULTS

Demographic data are shown in Table 1. Patients in the TBI group received significantly more cardioplegia solution and had a longer CPB time. The duration of aortic cross clamping was longer in the TBI group but this was not statistically significant.

Patients in the control group received one of four glucose management techniques according to anesthesiologist preference: no insulin (*n* = 54), bolus insulin (*n* = 33), insulin infusion (*n* = 52), and bolus plus infusion (*n* = 72). The mean (±SD) dose of insulin administered during CBP was similar in the TBI (21.9 (9.5) IU) and in the control (23.2 (16.0) IU) groups (*p* = .36).

The frequency of hyperglycemia, hypoglycemia, and severe hypoglycemia during the three periods are shown in Tables 2 and 3. The incidence of hyperglycemia during

**Table 2.** The frequency of hyperglycemia during CPB, following CPB, and during the first 6 hours in ICU.

	Treatment Group <i>n</i> = 211	Controls <i>n</i> = 211	<i>p</i> -Value
Hyperglycemia during CPB (%)	22 (10.5)	117 (55.5)	<.0001
Hyperglycemia after CPB (%)	37 (17.5)	37 (17.5)	1.00
Hyperglycemia in ICU (%)	5 (2.4)	14 (6.6)	.0337

CBP and in the first 6 hours in the ICU was significantly less in the TBI group compared with controls. The number of hypoglycemic episodes during all periods was 10 in the TBI group and eight in the control group (*p* = .63); the number of severe hypoglycemic episodes during all periods was one (.47%) in the TBI group and five (2.3%) in the control group (*p* = .09). The number of patients treated with 50% dextrose for hypoglycemia in the operating room was two in the TBI group and six in the control group. Treatment for hypoglycemia in the TBI group was per protocol if BG was below 3.5 mmol/L (63 mg/dL). In the control group, hypoglycemia was treated at the anesthesiologist's discretion.

## DISCUSSION

Our results indicate that the TBI technique is more effective in avoiding hyperglycemia in patients undergoing CPB with glucose-enriched cardioplegia compared with historical controls. Furthermore, the TBI technique was associated with low incidences of hypoglycemia and severe hypoglycemia. Interestingly, the average delivered dose of insulin was similar between the two groups, despite the fact that the control group included 54 patients who received no insulin at all.

**Table 3.** The frequency of hypoglycemia and severe hypoglycemia during CPB, following CPB, and during the first 6 hours in ICU.

	Treatment Group <i>n</i> = 211	Control Group <i>n</i> = 211	<i>p</i> -Value
During CPB			
Hypoglycemia (%)	2 (1)	2 (1)	1.00
Severe hypoglycemia	0	0	—
After CPB			
Mild hypoglycemia (%)	1 (.5)	0	—
Severe hypoglycemia (%)	1 (.5)	1 (.5)	1.00
ICU			
Mild hypoglycemia (%)	7 (3)	6 (2)	.7781
Severe hypoglycemia (%)	0 (0)	4 (1.9)	—

The CPB time and delivered cardioplegia dose were significantly higher in the TBI group. This difference would make the TBI group more prone to hyperglycemia but conversely may have been protective against hypoglycemia.

The question arises as to why the TBI method is effective in maintaining normoglycemia compared with the techniques used in the historical matched controls. The counter-regulatory milieu that develops during CPB is compounded by administration of glucose in the cardioplegia solution. We hypothesize that the delivery of insulin to the effect-site before the onset of CPB results in receptor activation and sustained activity before the deleterious effects on glucose homeostasis associated with CPB and dextrose administration (in cardioplegia). In addition, bolus insulin administered at the time of aortic cannulation has a similar duration (i.e., 1–2 hours) as the period of increased glucose administration and CPB, resulting in effective glucose control during CPB while not causing hypoglycemia in the postoperative period.

We speculate alternative strategies used in our unit fail because insulin is delivered too late and/or in too small doses into a milieu of insulin resistance to be effective. TBI delivers insulin as a preventative strategy as opposed to the reactive nature of other methods used. Some clinicians do not attempt intraoperative glucose control because of the relative paucity of evidence for improved outcomes or the fear of causing inadvertent hypoglycemia.

The high incidence of hyperglycemia following CPB is concerning. This result may reflect the fact that the hyperglycemic effects associated with surgical stress and CPB outlasted the duration the short acting (Actrapid) insulin used. Future strategies will have to include ongoing vigilance and treatment of glucose throughout the intraoperative and postoperative period, while avoiding increasing the incidence of hypoglycemia.

This study has a number of limitations. The data are non-randomized and non-blinded, and therefore the results are subject to selection bias. The case-matched controls were obtained from a period preceding the TBI group. Furthermore, the controls were treated with a variety of insulin regimes. It is possible that sub-groups of patients in the control group had highly effective glucose control and a low incidence of hypoglycemia, which was not identified in this study. Case matching was imperfect and significant differences exist between the two groups with respect to the total cardioplegia volume administered and the CPB time. Although not statistically different, there was also a trend towards longer aortic cross-clamp times in the TBI group. Although significantly better than the controls, the incidence of hyperglycemia in the TBI group was 10.5%, which is concerning. Patient numbers are insufficient to determine the risk factors for hyperglycemia with TBI. For instance, it is plausible that patients

with diabetes or greatly prolonged CPB are at risk of hyperglycemia even with the TBI technique.

Despite the limitations of this study, we propose that the TBI technique is a simple, safe, and effective technique for controlling blood glucose during CPB with glucose containing cardioplegia. The first of these benefits is particularly important, given that insulin regimes are often too complex and unwieldy to apply in day-to-day clinical practice. To determine the clinical significance of the TBI technique will require a suitably powered, randomized controlled trial.

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