Perioperative Glucose Control: *Is this hip or hype?*

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Learning Objectives:
1. To understand the cause of intraoperative hyperglycemia.
2. To review the adverse effects of hyperglycemia and potential benefits of insulin administration.
3. To discuss the evidence of adverse outcomes related to hyperglycemia in the perioperative period as well as the non-operative setting.
4. To review the evidence for improved outcomes with perioperative treatment of hyperglycemia.
5. To appreciate possible differences in insulin treatment for perioperative glucose control in diabetic patients compared to nondiabetics.

Case #1

A 74-year-old man with a history of coronary artery disease and mitral regurgitation, presents for a CABG and mitral valve repair. After an uneventful anesthetic induction and maintenance period, the patient is noted to have mildly elevated glucose levels.

1) Why is this non-diabetic patient becoming hyperglycemic?
2) What are some of the biochemical adverse effects of hyperglycemia?
3) What is the evidence that hyperglycemia may be detrimental in the non-operative setting?
4) What is the evidence that hyperglycemia may be detrimental in the perioperative period?

Patients who experience surgery, major trauma or illness often develop a hypermetabolic stress response characterized by hyperglycemia and insulin resistance. This response involves an increase in endogenous glucose production while insulin-stimulated peripheral glucose uptake is reduced. This condition is often referred to as “stress hyperglycemia” or “diabetes of injury” and occurs in diabetics and nondiabetics. Initially, this response was considered to be a beneficial adaption to critical illness since additional glucose was available as an energy source. However, recent evidence suggests that acute severe hyperglycemia may cause numerous adverse effects and serious adverse clinical outcomes. Alternatively, this patient may have underlying glucose intolerance, who is not yet diagnosed with diabetes. Approximately 29% of patients undergoing cardiac surgery have diabetes -- many of whom are undiagnosed.

Hyperglycemia incites numerous adverse events at the cellular and biochemical level, including endothelial dysfunction, oxygen radical formation, a pro-inflammatory response, and increased risk for infection. In animals, hyperglycemia increases myocardial infarct size and abolishes myocardial protection from ischemic preconditioning.

Clinical outcomes following illness are worsened by hyperglycemia. Hyperglycemia increases risk for early mortality, congestive heart failure, and cardiogenic shock, following acute myocardial infarction. Hyperglycemia increases risk of mortality and poor functional recovery after stroke. Hospitalized patients with hyperglycemia have worse outcomes.
Hyperglycemia is associated with worse outcomes after cardiac surgery, including increased risk of death\textsuperscript{6-8} and deep sternal wound infections.\textsuperscript{9} Peak glucose levels during CPB were associated with a three-fold increase in risk for mortality.\textsuperscript{8} Preoperative\textsuperscript{10} and postoperative\textsuperscript{9} hyperglycemia increased risk for deep sternal wound infections. Poor intraoperative glycemic control was associated with increased in-hospital mortality and increased cardiovascular, respiratory, neurologic, and renal morbidity.\textsuperscript{7,8,11} Importantly, these studies were observational; thus, it remains possible that perioperative hyperglycemia is simply a marker for illness severity rather than an independent predictor of outcome.

Soon after commencement of CPB, the patient’s serum glucose rises significantly. The arterial blood gas glucose values measurements rise to 236, 268, and 287 mg/dL. Aggressive treatment with IV insulin boluses is initiated.

4) What factors specific to CPB contribute to intraoperative hyperglycemia.
5) What evidence suggests that treatment of hyperglycemia will improve outcomes?
6) Does intraoperative hyperglycemia matter?
7) What are the potential beneficial effects of insulin administration?
8) Regarding treatment of blood glucose levels, are LOWER glucose levels BETTER?

Hyperglycemia is common in patients undergoing cardiac surgery. “Stress hyperglycemia” is exacerbated by additional factors specific to cardiopulmonary bypass, including hypothermia\textsuperscript{12} and glucose-containing cardioplegia.\textsuperscript{13} Other factors include increased renal absorption of glucose, increased substrate availability in the form of lactate, and decreased exogenous insulin activity.\textsuperscript{14} The severity of the hyperglycemic response during cardiac surgery is affected by an individual’s ability to control blood glucose and the magnitude of surgery.\textsuperscript{16}

Multiple retrospective reports suggest that treatment of hyperglycemia will improve outcomes. Decreasing postoperative glucose to < 200 mg/dL decreased sternal wound infection rate\textsuperscript{9} and mortality by over 50%.\textsuperscript{6} Intensive insulin therapy in surgical critically ill patients decreased risk of death, sepsis, and renal failure.\textsuperscript{17} In medical critically ill patients, glucose control reduced kidney injury, duration of mechanical ventilation, and hospital stay.\textsuperscript{18} However, not all studies have shown a benefit with glucose control. A large multi-center study called VISEP (Efficacy of Volume substitution and Insulin therapy in severe SEPsisis), which assessed fluid resuscitation and blood glucose control, was aborted due to excessive hypoglycemia without a difference in mortality.\textsuperscript{19} Glucontrol was terminated early for similar reasons.\textsuperscript{∗}

Conflicting evidence has been reported regarding benefit of intraoperative blood glucose control. Diabetic patients who received tight perioperative glucose control (125 – 200 mg/dL) had higher cardiac indices, lower inotropic requirements, less atrial fibrillation, and shorter length of hospital stay compared to those receiving standard therapy (<250 mg/dL).\textsuperscript{20} In contrast, others found no risk reduction in cardiac surgical patients who received intra-operative glucose control (80 – 100 mg/dL) compared to a control group (insulin if >200 mg/dL).\textsuperscript{21} Unexpectedly, incidence of death (4 vs. 0; P = 0.061) and strokes (8 vs. 1; P = 0.020) were higher with tight glucose control. A meta-analysis of 34 trials that assessed effect of insulin infusion on outcomes found that mortality was lower (although data were inconclusive) and incidence of hypoglycemia was higher in patients with improved blood glucose control.\textsuperscript{22}

∗ ClinicalTrials.gov/Blucontrol Study: Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients. http://clinicaltrials.gov/show/NCT00107601
Unfortunately, hyperglycemia during cardiopulmonary bypass may be severe and is often difficult to control with conventional insulin therapy. One report described an aggressive insulin protocol to treat hyperglycemia during CPB. Despite large doses of insulin, treated and untreated patients became similarly hyperglycemic on CPB. Further, 40% of treated patients developed hypoglycemia postoperatively. Others were able to lower blood glucose during CPB; however, glucose levels on arrival to the ICU were similar between patients receiving insulin vs. placebo.

Insulin maintains normal cell metabolism by increasing glucose uptake and cellular ATP production. Insulin stimulates glucose oxidation and down-regulates myocardial free fatty acid oxidation. Insulin also has numerous nonmetabolic effects, including a reduction in endothelial dysfunction, which may prevent organ failure and death, and anti-inflammatory, anti-thrombotic, and anti-atherogenic effects. Insulin treatment causes arterial vasodilation, capillary recruitment, directly improves human myocardial perfusion. Insulin also has inotropic and cardioprotective effects.

Interestingly, surgical critically ill patients with mildly elevated blood glucose had an increased mortality and other complications suggesting that lower glucose levels (i.e., closer to normoglycemia) are better. In contrast, a large metaanalysis found no difference in outcome between critically ill patients with very tight (≤110 mg/dL) or moderately tight (<150 mg/dL) glucose control.

During 96 min of CPB, the patient experiences severe hyperglycemia (blood glucose between 236 - 312 mg/dL). The patient receives multiple IV boluses of insulin (total 48 units). The patient is weaned off of CPB requiring support with an epinephrine infusion. On ICU admission, the patient’s blood glucose is noted to be 42 mg/dL.

9) How is perioperative hypoglycemia recognized?
10) How should perioperative hypoglycemia be treated?
11) Is there anything wrong with erratic and widely variable glucose levels?
12) Should the target blood glucose level differ between diabetics and non-diabetics?

High doses of insulin increase a patient’s risk for postoperative hypoglycemia. Severe hypoglycemia may be demonstrated by somnolence, unconsciousness, seizures, and, after prolonged exposure, irreversible neurologic sequelae and/or death. Symptoms of mild to moderate hypoglycemia include dizziness, palpitation, restlessness, drowsiness, anxiety, blurred vision, slurred speech, abnormal behavior. However, anesthetized patients will not demonstrate the typical clinical signs of hypoglycemia. Thus, frequent blood glucose measurement is necessary.

Immediate treatment of hypoglycemia is indicated with intravenous dextrose followed by continued monitoring of blood glucose (every 15 min) to avoid recurrence of hypoglycemia.

Large swings in glucose values have been described as glucose variability. Increased glucose variability has been associated with adverse outcomes in critically ill patients. Glucose variability was a stronger predictor of ICU mortality than average glucose levels in critically ill patients, and decreased variability was associated with reduced ICU mortality.

Diabetics may require different glucose targets than nondiabetic patients. Diabetic critically ill patients, unlike other nondiabetics, received no mortality benefit from strict glucose control. Others found that diabetes significantly modified the relationship between glycemic control and survival, as similar mortality rates were seen in diabetic patients with higher glucose levels.
References


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