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Glycemic control and outcome related to cardiopulmonary bypass

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Perioperative hyperglycemia, aggravated by cardiopulmonary bypass, is associated with adverse outcome in adult and pediatric patients. Whereas hyperglycemia was originally perceived as an adaptive response to surgical stress, it is now clear that glycemic control is a strategy to reduce adverse outcomes after cardiac surgery and cardiopulmonary bypass. The optimal blood glucose target, whether or not glycemic control should be initiated already intraoperatively, and whether or not perioperative glucose administration affects the impact of glycemic control on ischemia–reperfusion damage remain open questions. Hypoglycemia, the risk of which is increased with glycemic control, is also associated with adverse outcomes. However, it remains controversial whether brief episodes of hypoglycemia, rapidly corrected during glycemic control, have adverse effects on outcome. This review gives an overview of the currently available literature on glycemic control during and after cardiac surgery and focuses on the indicated open questions about this intervention for this specific patient population.

Hyperglycemia in cardiac surgery patients

Hyperglycemia is a commonly occurring metabolic disturbance in patients who undergo cardiac surgery, whether or not suffering from preexisting diabetes mellitus [1]. The use of cardiopulmonary

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bypass (CPB) for cardiac surgery further disturbs glucose homeostasis and aggravates the hyperglycemic response [2]. Although any blood glucose value higher than the normal healthy range during cardiac surgery could be labeled as hyperglycemia, a clear definition of perioperative hyperglycemia is currently lacking [3]. However, the American Diabetes Association suggests defining any blood glucose value above 140 mg/dl (>7.8 mmol/l) in the perioperative phase as perioperative hyperglycemia [4].

Several factors contribute to the hyperglycemic response evoked by cardiac surgery, including the patient's predisposition, metabolic alterations induced by the injury of the surgery, and concomitant treatments. Patient's characteristics that predispose to a more severe hyperglycemic response include the presence of obesity, insulin resistance, hypertension, and an atherogenic lipid profile, which are all highly prevalent among cardiac surgery patients [5]. The development of a sort of "diabetes of injury" or "stress diabetes" during cardiac surgery is characterized by insulin resistance, which contributes to the degree of perioperative hyperglycemia [6]. The exact pathophysiology of this "stress hyperglycemia" is complex and reviewed extensively elsewhere [6]. Furthermore, several commonly used anesthesiologic interventions during cardiac surgery may disturb glucose metabolism. These include the administration of inotropes, vasopressors, glucocorticoids, heparin, beta-blockers, and the infusion of glucose [7].

The hyperglycemic response to surgery was long considered to be adaptive and beneficial. This was based on the assumption that high levels of circulating glucose would fuel the high glucose need of cells that predominantly rely on glucose as metabolic substrate and that can take up glucose independent of insulin, such as neurons, hepatocytes, endothelial cells, and blood cells. This viewpoint, however, contrasted with the clear association between hyperglycemia and increased morbidity and mortality as observed for critically ill patients [8–10] and cardiac surgery patients [11–13]. This evidence has recently been summarized in a systematic review [3]. These findings suggested that cardiac surgery-induced hyperglycemia, rather than being an adaptive response and reflecting the severity of the surgical procedure or pharmacological interventions, may contribute to complications. This alternative interpretation provided the rationale for lowering blood glucose concentrations during the perioperative period in cardiac surgery patients.

Glycemic control in cardiac surgery patients

Several studies have investigated the impact of lowering blood glucose concentrations in cardiac surgery patients. These are discussed separately for adult and pediatric patients in the following sections and summarized in Table 1.

Adult cardiac surgery patients

The first randomized controlled trial (RCT) to investigate the effect of lowering glycemia in the perioperative period was published in 2001 [14]. In this single-center study, 1548 adult patients were randomized to receive either intensive insulin therapy (IIT) in which insulin was infused to target blood glucose to the normal range of 80–110 mg/dl (4.4–6.1 mmol/l) or to conventional therapy with infusion of insulin only when glucose concentrations exceeded 215 mg/dl (11.9 mmol/l). The latter was the standard of care at that time for patients admitted to the surgical intensive care unit (ICU). In this study, 63% of the patients were admitted to the ICU after cardiac surgery. IIT reduced mortality of the total group of ICU patients, as well as of the cardiac surgery subgroup [15]. In the latter subgroup, the mortality benefit was maintained up to 4 years after hospital discharge. Morbidity of the cardiac surgery patients was also reduced, most pronounced for patients who stayed more than 3 days in the ICU, as indicated by earlier weaning from mechanical ventilation, less acute renal failure, reduced incidence of critical illness polyneuropathy, reduced inflammation, and shorter ICU stay [15]. Similar findings have been reported in observational studies by Furnary et al. [16] In these studies, 3554 patients with preexisting diabetes mellitus who underwent coronary artery bypass grafting (CABG) between 1987 and 2001 were described. These reports showed a 50% decrease in perioperative mortality and a significant decrease in the incidence of deep sternal wound infections in patients receiving continuous insulin infusion with a blood glucose target of 100–150 mg/dl (5.6–8.3 mmol/l). The authors further expanded the patient cohort between 2001 and 2005 to include an additional 1980 patients [17]. In this study, a tighter glycemic control resulted in a decreased incidence of deep sternal