Review Article

Glucose Homeostasis during the Perioperative Period of Cardiac Surgery: A Narrative Review

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Abstract

Hyperglycemia and insulin resistance are frequent in intensive care patients and have been associated with worse outcomes. The control of blood glucose levels has an impact on the morbidity and mortality of intensive care patients. The authors focused on the perioperative period of cardiac surgery and reviewed the various mechanisms that contribute to hyperglycemia, such as surgical trauma, heparinization, cooling, rewarming and cardioplegia. The consequences of perioperative hyperglycemia in terms of morbidity and mortality, and the possible management strategies (including GIK, GIN and normoglycemic hyperinsulinism) were also reviewed.

Keywords: Hyperglycemia; Glucose Homeostasis

1. Introduction

Hyperglycemia and insulin resistance are frequent in intensive care and are associated with severe outcomes. Blood glucose control has an impact on the morbidity and mortality of intensive care patients [1]. The authors focused on the perioperative period of cardiac surgery and reviewed the different

mechanisms, consequences, and management possibilities of perioperative hyperglycemia.

2. Mechanisms of Hyperglycemia

2.1 Surgical trauma

Hyperglycemia is a normal metabolic response to major surgical trauma. During cardiac procedures, this reaction is severe with blood glucose levels exceeding 10 mmol/L even in the absence of diabetes mellitus [2]. Upon induction, catecholamine levels increase and following incision there is an increase in the levels of ACTH, cortisol, and growth hormone. It has been shown experimentally that by adding epidural analgesia to general anesthesia, the nociceptive stimuli are decreased in intensity with a measured decrease in the levels of cortisol, catecholamine, and growth hormones [4, 5]. Pain stimuli can enhance glucose production via cortisol, catecholamine, and growth hormones.

2.2 Heparinization

Injection of lipid-heparin causes the release of lipoprotein lipase present on the surface of endothelial cells [6]. Free fatty acids (FFAs) have been shown to decrease glucose uptake by cardiac muscle and the diaphragm [7]. FFAs inhibit the use of glucose by the muscles by blocking its transport and by inhibiting glycolysis and oxidation of pyruvate [8]. FFAs also stimulate gluconeogenesis from lactate, alanine, and pyruvate [9]. In an "euglycemic clamp technique" study of ten healthy subjects, the infusion of lipid-heparin with an unchanged insulin flow rate increased glucose production and decreased its use [10]. The infusion of lipid-heparin induced a state of insulin resistance [10].

2.3 Hypothermia

The levels of glucose and hormones involved in carbohydrate homeostasis have been studied in 12 patients undergoing cardiopulmonary bypass (CPB) in hypothermia versus in normothermia [11].During hypothermia there was an up to 46%increase in blood glucoselevels by the end of CPB. The glucose level was increased to 154 ± 20 mg/dL, with a decrease in insulin and an increase in adrenaline despite a decrease in cortisol and growth hormone. The average blood glucose level reached 271 ± 30 mg/dL in the hypothermia group vs 221 ± 51mg/dL in the normothermia group by the third post-operative hour [11]. Hypothermia inhibits the production of glucose by the liver during CPB to such an extent that more glycogen can be converted into glucose after CPB [12].

2.4 Rewarming

During rewarming the insulin concentration increases to twice the preoperative value. Despite this, the blood glucose level increases as a result of a simultaneous increase in the levels of hyperglycemic hormones, in particular glucagon[11].After rewarming, cortisol and growth hormone levels are higher than in the normothermia group [12, 13]. During rewarming a 28% increase in blood glucose levels has been shown to be accompanied by a 374% increase in insulin levels, suggesting a form of insulin resistance [11].This phenomenon is partly explained by the concomitant increase in the levels of noradrenaline, glucagon and cortisol by 20, 58 and 34 percent respectively [11].

2.5 Cardioplegia

The type of cardioplegia can influence blood glucose control. An international survey of 983 anesthetists around the world showed that the addition of glucose to cardioplegia solutions differed between regions: Europe 17.9%, North America 53.3%, Australia/New Zealand 16.7%, and South America 40.4% [14].

During cardioplegia the mean interstitial glucose level remains higher than 1 mmol/L [15]. The low temperature reduces or abolishes the capture of interstitial glucose [15]. The hypothesis is that glucose and insulin activate glycolysis and slow down the depletion of adenylated nucleotides [16]. Glucose seems to have a protective effect by direct action on the membranes of cardiomyocytes [17]. However, adding glucose to cardioplegia solutions does not seem to have an effect on the patient's postoperative outcome [18]. The addition of glucose to cardioplegia solutions can increase the patient's blood glucose level and disturb glucose homeostasis.

3. Consequences of Hyperglycemia

3.1 Inotropic support

Hyperglycemia is a part of post-operative low cardiac output syndrome. A phenomenon of ischemic preconditioning is believed to occur in which activation of KATP channels results in resistance to prolonged ischemia [19]. However, in an animal model, it has been shown that hyperglycemia blocks this channel and abolishes intraoperatively the effect of ischemic preconditioning [20]. This ischemic preconditioning present in patient candidates for CABG potentially leading to more hemodynamic instability if he is altered. It has also been shown that hyperglycemia exaggerates ischemia-reperfusion-induced cardiomyocyte injury via endothelin-1 [21]. In addition, during ischemia, glucose is the preferred substrate of the myocyte. However, insulin resistance results in hyperglycemia and a decrease in glucose uptake. The mechanism is then turned towards glycolysis which consumes more oxygen and produces more FFAs. A high level of FFAs inhibits the oxidation of glucose and impairs the recovery of mechanical function and cardiac efficiency during reperfusion [22]. Hyperglycemia results in defects in the formation of nitric oxide [23], increased radical oxygen species production, endothelial dysfunction and decreases in wall shear stress [24].

3.2 In-hospital death

A retrospective study of 6280 cardiac surgery patients (1579 diabetic and 4701 non-diabetic) was undertaken to assess the influence of hyperglycemia during CPB on perioperative morbidity and mortality [25]. Each patient was seen preoperatively by their cardiologist or general practitioner and several blood glucose levels were measured to reduce the risk of having unrecognized diabetes. The authors observed a mortality of less than 2% when the peak serum glucose level was below 20 mmol/L (360 mg/dL). The mortality incidence was multiplied by 3 when the peak exceeded this value. The peak blood glucose level was an independent factor of mortality in non-diabetic patients (odds ratio [OR] 1.12,95% confidence interval [CI]1.06-1.19, p <0.001) and in diabetic patients (OR 1.20,95% CI 1.08-1.32, p = 0.0005) [25]. In a series of 3554 diabetic patients submitted to CABG there was a direct link between any episode of glycemia above 175 mg/dL and mortality on the day of the intervention (OR 1.006 per 1 mg/dL, p <0.003), on the first postoperative day (OR 1.013 per 1 mg/dL, p <0.001) and on the second postoperative day (OR 1.013 per 1 mg/dL, p <0.015) [26]. In another study, the first postoperative blood glucose level was measured in a cohort of 2297 consecutive CABG patients, 836 of whom were diabetic [27]. They showed that an episode of postoperative glycemia greater than 200 mg/dL was an independent risk factor for mortality at 30 days with an OR of 13.01 (95% CI 2.61-65.34, p = 0.002) in the non-diabetic patient but not in the diabetic patient with an OR of 3.37 (95% CI 0.43-26.58,p = 0.249) [27]. The meaning is different in the diabetic patient and the non-diabetic. In diabetic patients, the postoperative blood glucose level reflects the severity

of their diabetes, which is a marker of more comorbidity and greater insulin resistance [28].

3.3 Pulmonary complications

An association has been demonstrated between poor glycemic control and the occurrence of pulmonary and infectious complications in non-diabetic patients [29]. A 1:3 case:control study of patients who developed ventilator-associated pneumonia (VAP) after cardiac surgery (57 patients vs 149 control) showed that arise in blood glucose levels before surgery was an independentrisk factor of having a postoperative VAP (OR 1.008, 95% CI 1.000-1.015, p = 0.043) [30]. Another study of 2215 patients post-CABG found that major adverse events (MAEs, including VAP) occurred in 260 patients (11.7%) and were associated with increased mean postoperative glucose levels in the first 24 hours (OR 1.017, 95% CI 1.010-1.024, p <0.001) [31]. These two studies have in common that the occurrence of VAP was related to hyperglycemia but was independent of glycosylated hemoglobin levels.

3.4 Infectious complications

Hyperglycemia induces reduced neutrophil activity (e.g., chemotaxis, formation of reactive oxygen species) despite accelerated diapedesis of leukocytes into peripheral tissue [32]. Hyperglycemia also increases concentrations of the early proinflammatory cytokines tumor necrosis factor-alpha and interleukin-6. Furthermore, a reduction of endothelial nitric oxide formation occurs, along with a reduction in the microvascular reactivity to dilating agents such as bradykinin. Complement function (e.g., opsonization, chemotaxis) is also impaired, despite elevations of certain complement factors [32]. Hyperglycemia causes direct glycosylation of proteins and alters the tertiary structure of complement resulting in inhibition of immunoglobulin-mediated opsonization of bacteria and complement fixation to bacteria and decreased phagocytosis [33]. These factors promote the development of pneumonia, wound infection and mediastinitis. Glycemic control has been shown to decrease the risk of wound infection and mediastinitis [34, 35].

3.5 Renal complications

Hyperglycemia-induced endothelial dysfunction is associated with an inflammatory process and disruption of renal hemodynamics [32].This endothelial dysfunction contributes at the microvascular level to the extension of renal injury at the tubular level [36]. Vascular congestion, edema formation, diminished blood flow, and infiltration of inflammatory cells have been documented in the corticomedullary junction of the kidney [36]. Hyperglycemia impairs renal autoregulation and glomerular filtration rate through a tubule glomerular feedback mechanism [37]. A retrospective study of 880 patients who underwent off-pump coronary artery bypass graft (OPCAB) examined the relationship between intraoperative blood glucose levels and post-operative acute kidney injury (AKI) [38].Multivariate analysis of the data identified three independent risk factors for postoperative AKI: glucose> 150 mg/dL (OR 2.78, 95% CI1.12-6.86, p = 0.027), the coefficient of variation of glucose (OR 1.04, 95% CI 1.01-1.07, p = 0.027) and preoperative serum creatinine> 1.4 mg/dL (OR 8.81,95% CI 3.90-19.9, p<0.001) [38].

3.6 Neurological complications

Poor glycemic control has been shown to be associated with the occurrence of neurological complications[29]. The presence of diabetes increases the risk of the occurrence of neurological complications by 63% (p = 0.003). This phenomenon

is partly linked to a mixture of ischemia reperfusion and endothelial dysfunction induced by hyperglycemia [32]

4. Management of Hyperglycemia

4.1 The glucose-insulin-potassium solution (GIK)

In 1962, a GIK solution (20 mEq of KCl, 20 units of regular insulin and 1000 cc of a 5-10% glucose solution) was used for the first time in humans [39].The solution was used in acute myocardial infarction in order to restore the potential of still-viable ischemic cell membranes, with an improvement observed on the EKG [39]. Fifty years later, a meta-analysis of 16 randomized controlled studies showed no benefit of GIK in infarction with ST-segment elevation when thrombolysis or coronary reperfusion data were included [40]. The use of GIK in cardiac surgery is controversial. A randomized GIK versus placebo-controlled study was conducted on 224 patients undergoing elective aortic valve replacement and/or CABG [41]. GIK pretreatment was found to be associated with a reduced occurrence of low cardiac output syndrome (LCOS) (RR 0.28, 95% CI 0.14-0.53). Patients pre-treated with GIK also had a significantly lower troponin level on postoperative day one (2.9 ng/mL [1.5-6.6] vs 4.3 ng/mL [2.4 - 8.2], p = 0.009) [41].Similarly, the Hypertrophy, Insulin, Glucose, and Electrolytes (HINGE) trial, which involved 217 patients undergoing aortic valve replacement for aortic stenosis, showed a significant reduction in the incidence of LCOS and the need for inotropes in the group treated with GIK [42]. Two randomized controlled studies on 930 and 224 patients undergoing CABG have shown a benefit of GIK treatment in regards to reducing the incidence of LCOS [43, 44]. A study of 44 patients undergoing CABG showed a decrease in plasma levels of FFAs but failed to show any clinical benefit [45]. Another two randomized controlled studies on 82 and 46 patients undergoing OPCABG showed no benefit from the administration of GIK when compared with placebo [46, 47]. GIK continues to be used in many countries around the world and is still under study [47].

4.2 Intensive insulin therapy

In 2001, the first randomized controlled trial of intensive glucose control was performed on 1548 patients admitted to a surgical intensive care unit (ICU) of a single hospital [48]. Sixty percent of these patients had been submitted to cardiac surgery. In the conventional treatment group, the patients received a continuous infusion of insulin (50 IU rapid insulin diluted in 50 ml of 0.9% NaCl)which was commenced if the blood glucose level exceeded 11.9 mmol/L, aiming to maintain a value of between 10.0 and 11.1 mmol/L. In the intensive treatment group, insulin was started when the blood glucose level exceeded 6.1 mmol/L, with a target value between 4.4 and 6.1 mmol/L. The authors observed a reduction of 42% in ICU mortality (95% CI 22-62, p <0.04) [48]. This effect was linked to the reduction in hyperglycemia rather than to the action of insulin per se [49]. The largest randomized controlled study to date on intensive insulin therapy, NICE-SUGAR, was a multicenter study (42 centers) involving 6104 patients, 3054 of whom were assigned to undergo intensive glucose control and 3050 to undergo conventional glucose control [50]. A total of 829 patients (27.5%) in the intensive-control group and 751 patients (24.9%) in the conventional-control group died (OR for intensive control 1.14, 95% CI 1.02 - 1.28,p = 0.02). Severe hypoglycemia (blood glucose level ≤ 2.2 mmol/L) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 patients (0.5%) in the conventional-control group (p<0.001) [50]. This study led to a

change in the guidelines to a blood glucose target value of between 7.8 and 10 mmol/L [51].The authors of NICE-SUGAR subsequently showed that the association of hypoglycemia with death followed a dose-response relationship, with a significant risk of death from distributive shock (HR 4.35, 95% CI 2.49-7.61, p <0.001) [52]. Several studies have shown the lack of benefit of intensive insulin therapy compared to conventional treatment in CABG [53-56].

4.3 Hyperinsulinemic normoglycemia

Several studies have tested the hypothesis that the administration of a high dose of insulin while maintaining normal blood glucose levels ("GIN therapy") may have beneficial effects in patients undergoing CABG. In one study, forty patients were randomized to receive either GIN therapy or sliding-scale insulin [57]. The study showed a benefit of GIN therapy in terms of improvement of the overall and systolic function of the left ventricle after CABG [57]. Another randomized controlled study of 99 patients undergoing CABG showed a gain in terms of a reduction in the plasma levels of FFAs and improvement of cardiac function [58]. A two-center study on 1409 cardiac surgery patients demonstrated a composite reduction in 30-day mortality and the onset of serious complications in the hyper insulinemic normoglycemia group, though a disparity in outcomes between the two centers complicates interpretation of the results [59]. The same author had previously demonstrated the lack of effect of GIN during cardiac surgery in a cohort of 100 patients [60]. Further studies would be needed to promote GIN as a potential treatment in cardiac surgery.

4.4 Glucose variability

A retrospective study on 2215 patients who underwent CABG showed that a variation in glycemia beyond a standard deviation was associated with a risk of major adverse event (OR 1.22, CI% 95 1.09-1.37, p <0.001). This study did not find any link with glycosylated hemoglobin [31]. an absence of association with glycosylated hemoglobin had already been found in patients with impaired renal function in another study [38].

5. Conclusions

The management of blood glucose levels during the entire perioperative period in cardiac surgery is of capital importance in terms of morbidity and mortality. It appears that it is necessary to avoid hyperglycemia,hypoglycemia and probably also large variations in blood glucose levels. Based on current evidence, a blood glucose level of 10.1 mmol/L is the threshold at which to initiate insulin. Normoglycemic hyperinsulinism may be of interest but there is a need for larger multicenter randomized controlled studies to assess its potential role.

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Not applicable.

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Competing Interests

The authors declare that they have no competing interests

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