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Chapter

Perioperative Glycemic Control for Patients Undergoing Coronary Artery Bypass Grafting

Cheng Luo, Chuan Wang, Xiaoyong Xie and BaoShi Zheng

Abstract

Coronary artery bypass grafting (CABG), as a gold standard treatment for coronary artery disease, has been widely adopted all around the world. Meanwhile, it’s also well known that diabetes is an independent risk factor for postoperative mortality. However, hyperglycemia often occurs perioperatively, regardless of whether the patient has diabetes or not. Perioperative stress hyperglycemia is harmful to patients undergoing cardiac surgery and has a clear correlation with increased inflammatory response, and clinical adverse events, especially for patients with diabetes. Thus, proper perioperative blood glycemic control can reduce the short-term and long-term mortality and the incidence of complications in patients undergoing CABG.

Keywords: coronary artery disease, diabetes mellitus, mortality, complications, glycemic control

1. Introduction

With the development of society and environment, the number of patients with coronary artery disease (CAD) is increasing, and a large number of patients have diffuse CAD, especially in patients with diabetes. Conservative treatment or interventional therapy is difficult to achieve satisfying results. Coronary artery bypass grafting (CABG) plays an irreplaceable role in the treatment of cardiovascular disease, but with larger trauma requiring thoracotomy. It is easy to develop stress hyperglycemia in both diabetic patients and non-diabetic patients. Previous studies have proved that hyperglycemia is an independent risk factor for increased postoperative mortality and complications. In addition to primary lesions, the risk of cardiovascular complications caused by diabetes may increase by 2–4 times. About 5.2% of CABG patients may have diabetes without preoperative diagnosis. Perioperative glycemic control also affects the prognosis of CABG, as a result, it is important for most patients to control blood glucose regardless of whether they are diagnosed with diabetes.
2. Mechanism of hyperglycemia after CABG

Cardiac surgery is prone to stress response, which is mainly caused by the massive release of neuroendocrine hormones, high catabolism, heat production and hyperglycemia. Diabetic patients suffer from insulin resistance (IR) due to the loss of sensitivity to insulin at physiological level. The intensive stress reaction increases IR after operation, which is characterized by pathological hyperglycemia, impaired glucose tolerance, increased lipolysis and hyperinsulinemia, which may cause a series of metabolic disorders and increased burden on the heart and lungs [1]. In addition to hyperglycemia, IR also has an impact on fat and amino acid metabolism by accelerating its catabolism and presents with clinical hyperlipidemia and negative nitrogen balance. Postoperative IR is a special metabolic state similar to type 2 diabetes after operation. The body’s biological response to insulin is weaker than normal, and it can also occur in patients with elective surgery without diabetes. Stress hyperglycemia (SH) is an independent risk factor affecting the prognosis and is directly related to the poor prognosis of elderly patients who underwent cardiac surgery [2]. During the CABG operation, whether patients are diabetic or undergoing cardiopulmonary bypass (CPB), especially in the absence of exogenous insulin, significant increases in blood glucose may occur, leading to various causes of hyperglycemia.

2.1 Surgical trauma

CABG with thoracotomy is a great stimulus, which may cause the hormone levels to lose balance, resulting in reactive hyperglycemia. The operation process will directly promote the production of some stress hormones (such as catecholamine, glucocorticoid, glucagon and growth hormone), in which the secretion of glucocorticoid is more than 10 times higher than usual. These are antagonistic hormones of insulin, which can promote glycogenolysis, liver gluconeogenesis, fat and protein catabolism, while inhibiting insulin release, reducing tissue sensitivity to insulin and increasing peripheral tissues’ IR, and thus, leads to a decreased glucose utilization, increased liver glycogen output and increased blood glucose reactivity [3]. The surgery process can also promote the production of a large number of cytokines and inflammatory mediators (such as tumour necrosis factor, interleukin-1 and interleukin-6), which will increase the secretion of the above stress hormones, resulting in decreased insulin secretion, increased IR and impaired glucose utilization, resulting in reactive hyperglycemia. Due to the decreased responsiveness and sensitivity of peripheral tissues to insulin, patients with surgical stress reactions cannot generate normal biological effects under a normal dose of insulin, with the IR and hyperglycemia coexisting with hyperinsulinemia [4]. It is generally believed that the molecular biological mechanism of IR is related to abnormal pre insulin receptor function, disorders of post insulin receptor signal transduction, glucose transport, intracellular metabolism and inflammation cytokines (such as tumour necrosis factor).

2.2 SH produced by CPB

Coronary artery disease (CAD) complicated with valve disease and other heart diseases usually requires revascularization under CPB, and factors such as hypothermia, hypotension, hemodilution, non-pulsatile perfusion and anaesthesia may cause strong stimulation during the surgery. The resulting strong reaction can increase the
concentration of glucose, free fatty acids, glycerol and lactic acid in blood, inhibit the phosphorylation of insulin in peripheral tissue cells, insulin receptor substrate-1 and cell division activated protein kinase and produce IR and abnormal glucose tolerance [5]. At the same time, the increase of adrenocortical hormone caused by stress can also indirectly aggravate hyperglycemia and IR. The mechanisms are as follows: (1) pre receptor: increased secretion of catecholamine, growth hormone, cortisol and glucagon to resist the hypoglycemic effect of insulin; (2) receptor: the down-regulation of the number of receptors and the decrease of the binding rate between insulin and receptors; (3) Post receptor: the activity of insulin substrate decreases and the number of glucose transporters decreases. In addition, a series of stimulation of CPB can promote the generation of endogenous blood glucose, reduce the uptake of blood glucose by tissues, and strengthen the reabsorption of glucose filtered in original urine by kidneys, so as to increase blood glucose.

CPB aggravates postoperative IR in patients with CABG and increases glycemia in both diabetic and nondiabetic patients [6]. It makes glycemic control more difficult in the early postoperative period, which is significantly associated with early mortality and morbidity. For patients with diabetes mellitus and poor coronary artery condition, it is off-pump CABG operation (which performs CABG without CPB) might be an alternative option. Meanwhile, surgeons should always pay attention to the risk and risk factors of postoperative hyperglycemia and insulin resistance and reduce insulin resistance and postoperative blood glucose level to promote postoperative recovery.

2.3 Psychosocial factors

In addition to physical stress, patients also have psychosocial stress perioperatively, such as fear or even anxiety. As a result, a series of physiological changes (such as rapid heartbeat, increased sweating, etc.) will occur, which may be caused by the increased excitability of sympathetic nerve and the imbalance of autonomic nervous system. Sympathetic nerve excitation will lead to the increased secretion of glucocorticoids such as adrenal hormone, which will increase blood glucose. Therefore, the psychological state is also an important factor affecting the perioperative blood glucose stability, and it plays an important role in the occurrence and development of SH.

2.4 Other factors

Topical drugs during surgery are also one of the factors leading to SH, such as catecholamines, cyclosporine, steroids, diuretics, protein inhibitors, growth hormone, etc. These drugs can also affect glucose metabolism and cause reactive hyperglycemia.

3. The danger of hyperglycemia

3.1 Damage to heart

Hyperglycemia damages almost all organs, especially the heart. The study found that the incidence of postoperative complications of non-diabetic patients with unsatisfactory glycemic control was significantly higher than that of patients with ideal glycemic control, and the prognosis was even worse. SH will affect the immunity of patients undergoing cardiovascular surgery and reduce the anti-infection ability.
SH can not only inhibit the phagocytosis and chemotaxis of autoimmune cells and neutrophils but also destroy the structure of cells and increase the permeability of cell wall, thus affecting the function of cells [7]. SH makes the blood become viscous, with red blood cells and platelets gathered, causing blood hypercoagulability and gradually forming thrombosis. Free radicals aggravate oxidation, produce a large number of lipid peroxides in the blood and adhere to the vessel wall, making the blood vessel cavity thinner, the pipe wall rough, the elasticity weaker and the blood vessel brittle, thus increasing the incidence of cardiovascular events. It is found that the level of blood glucose is positively correlated with the size of myocardial infarction area [8]. The higher the blood glucose level is, the higher the infarct size is. The damage of SH to the heart is mainly manifested in the following aspects.

3.1.1 Increase inflammatory response

In 2002, Esposito et al. reported that in the experiment of healthy patients and diabetics or patients with impaired glucose tolerance, the increase of stress blood glucose could lead to a sharp increase in inflammatory markers and increase the release of inflammatory factors, thereby aggravating the inflammatory response. In 2003, marfella et al. found that SH was positively correlated with enhanced inflammatory immune response and could worsen cardiac function. All the above show that SH can exacerbate inflammatory response and reduce cardiac function.

3.1.2 Aggravate the edema of ischemic cardiomyocytes

During CPB, the myocardial ischemia and hypoxia are more obvious, which accelerates the anaerobic glycolysis of glucose, resulting in the increase of the end products of lactic acid, and the permeability of the vascular wall, and thus, forming the edema with the retention of sodium and water [9]. Meanwhile, hyperglycemia also slows down the recovery of calcium ions, resulting in a large amount of calcium ions accumulation in cells, interfering with the process of mitochondrial oxidative phosphorylation, causing disorders of cellular protein and lipid metabolism, and inhibition of sodium and potassium pump. This obstacles of ATP production, and further aggravates the edema of ischemic cardiomyocytes.

3.1.3 Cause decreased cardiac function

SH can reduce cardiac function. Previous studies pointed out that hyperglycemia is significantly related to heart failure and is the main factor affecting the prognosis [10]. When the body is in a state of stress, SH can aggravate myocardial cell injury, increase infarct area, and weaken myocardial contractility with an expansion of necrotic area and ventricle, resulting in ventricular remodelling and increased myocardial oxygen consumption, and further aggravating myocardial ischemia and the risk of heart failure. A remarkable increase in blood glucose caused by excessive stress can lead to the change of hemodynamics, the increase of blood viscosity, aggravating the ischemia and the cardiac insufficiency.

3.2 Effect on prognosis of CABG

Diabetes mellitus (DM) has resulted in an increase in mortality after CABG. The mortality rate of patients without history of diabetes but with perioperative
hyperglycemia is also increased. The results of several studies on different glycemic control schemes show that the occurrence of intraoperative and postoperative hyperglycemia is positively correlated with the postoperative mortality [11], whether, patients undergo CPB or not during CABG. Blood glucose > 270 mg/dl during CPB is defined as hyperglycemia. The general treatment is a single injection of insulin. However, there is no standardized scheme. For diabetic and non-diabetic patients, intraoperative hyperglycemia is an independent predictor of morbidity and mortality. Relevant studies have shown that if the blood glucose for four consecutive measurements are all > 200 mg/dl, then the glycemic control effect is defined as poor. Compared with patients without hyperglycemia during operation, it can increase the in-hospital mortality and prolong the stay in ICU. Another study confirmed that the average and maximum blood glucose during CABG is one of the independent predictors of short-term postoperative mortality [12]. The average blood glucose during CABG is an important predictor of mortality, pulmonary and renal complications, and it increases the risk of retrosternal wound infection; Meanwhile, DM before CABG is an important risk factor for mortality.

3.3 Complications related to hyperglycemia

Elevated blood glucose will cause changes in body fluid osmotic pressure and affect cell function. The most important effect of hyperglycemia is perioperative infection. Many studies have shown that patients who underwent CABG complicated with hyperglycemia have a significantly increased risk of serious infection, including not only surgical process-related infections (mediastinal infection and wound infection) (Figure 1), but also urinary tract infections [13]. Diabetic patients are more likely to develop these complications. The risk of infection after CABG is 4 times higher in patients with DM. Although the specific reasons for the increased risk of infection are not yet clear, this may be related to chronic diseases. For example,
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long-term hyperglycemia leads to disorders of the immune system and local hypoxia caused by small vessel diseases. Other studies have also shown that the complications of infection in patients with postoperative hyperglycemia may be based on acute and reversible immune dysfunction, including the weakening of polynuclear bacteriophage and bactericidal effect [14]. Continuous insulin infusion for 24 hours postoperatively can restore the leukocyte function to the baseline level. It has been confirmed that postoperative hyperglycemia will reduce the chemotaxis, conditioning and overall antioxidant effect of lobulated nuclear leukocytes. Although the optimal dose and timing of insulin are unclear, insulin injection can reverse the changes in the immune system.

4. Glycemic control

4.1 Management of perioperative hyperglycemia

Compared with standard insulin therapy, continuous perioperative insulin infusion in cardiac surgery can significantly reduce the mortality by 57%, especially in patients with confirmed hyperglycemia. Lazar et al. found that the GIK of glucose + insulin + potassium before and 12 hours after operation can improve myocardial metabolism [15]. There was no significant difference in the 30-day mortality rate between the study group (glycemic control target at 6.9–11.1 mmol/l) and the control group (glycemic control <13.9 mmol/L), but the 2-year survival rate increased significantly. Lecomte et al. found that intensive glycemic control can reduce the 30-day mortality rate in patients without DM [16]. Most scholars believe that the target blood glucose level of cardiac surgery should be more restrictive.

4.2 Preoperative glycemic control

Preoperative blood glucose level includes fasting blood glucose level at admission, HbA1c level and average fasting blood glucose level 3 days before operation, which has different effects on mortality and cardiovascular-related adverse events. Schmeltz et al. found that the 30-day mortality rate of patients with DM after CABG was 2 times higher than that of non-diabetic patients, but there was no significant correlation between postoperative blood glucose and mortality [17]. Faritus et al. showed that the higher the HbA1c level before CABG, the higher the risk of incidence of postoperative infections [18].

4.3 Intraoperative glycemic control

Schwarzer et al. noticed that the increase of blood glucose during CPB cardiac surgery is an independent predictor of mortality during hospitalization [19]. With the increase of every 1 mmol/L, the mortality rate of diabetic patients will increase by 20%, while the mortality of non-diabetic patients will increase by 12%. The study also showed that when blood glucose was > 5.6 mmol/l, the postoperative adverse events increased by 34% for every 1 mmol/L increase in blood glucose. Ouattara et al. found that poor glycemic control during operation can increase 6.2 times of adverse events during hospitalization. The ideal method of intraoperative glycemic control remains unclear. Related studies showed that intensive insulin therapy did not reduce the time of hospitalization or ICU stay in patients with CAD combined with diabetes, and the
effect of intraoperative intensive insulin therapy had no obvious advantage compared with that of postoperative intensive insulin (PII) therapy.

4.4 Postoperative glycemic control

Postoperative stress hyperglycemia can significantly increase the mortality and adverse cardiovascular events. Related studies showed that severe hyperglycemia within 24 hours after CABG was significantly correlated with in-hospital mortality. In 2012, Desai et al. completed the prospective randomized controlled trials of insulin treatment for severe patients [20]. The results showed that PII treatment can reduce the mortality rate within one year, and can significantly reduce the mortality of patients with more than 5 days in ICU. In addition, it is also conducive to improving the quality of life. Meanwhile, PII reduced the incidence of hematogenous infection by 46%, the incidence of dialysis and hemofiltration by 41%, the average transfusion volume by 50%, and the incidence of severe multiple neuropathies by 44%. The results also found that in ICU, the treatment scheme of glycemic control in the surgical group and the non-surgical group treated with drugs brought significantly different results. Similar studies have shown that PII therapy can reduce the mortality of ICU patients, but no significant results were found for simple diabetic patients with the intensive insulin therapy. For diabetic patients, intensive insulin therapy can reduce the incidence of complications, including acute kidney injury and multiple neurological diseases. However, it is still lacking supportive data for the ideal control target of blood glucose as well as the therapy.

5. Perioperative intensive insulin therapy

5.1 Intensive insulin therapy after CABG

Based on the results of the above research and the understanding of the risk factors related to hyperglycemia and hypoglycemia, many perioperative insulin treatment schemes for CABG patients have been proposed. Although these data come from different patient groups, there is a consensus that it is beneficial to closely monitor blood glucose levels and optimize blood glucose data. Due to the different treatment schemes obtained from various literature and research projects, it is difficult to determine the ideal treatment scheme for glycemic control in patients undergoing CABG. Some studies only recommend the treatment guidelines for glycemic control in ICU patients after cardiothoracic surgery, while others provide specific schemes for hyperglycemia treatment. In these studies, a targeted program has successfully reduced the incidence of hypoglycemia [20]. Although some studies have shown that intensive glycemic control is reasonable and the occurrence of hypoglycemic events can be minimized through close glycemic control, no study can provide a specific treatment scheme for clinical use. Most patients use glucose injection and insulin injection to maintain it in a predetermined range by adjusting the injection ratio. Most studies reported that the adjustment of the predetermined blood glucose range reduced the incidence of hypoglycemia, and the commonly recommended blood glucose range was 100–150 mg/dl. In order to achieve the goal, blood glucose must be closely monitored in the operating room and ICU, and it is often required to measure blood glucose at the bedside every hour. Insulin injection therapy is very labour-consuming to monitor and adjust insulin dose at the same time, especially
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when strictly controlling blood glucose. Therefore, we should determine the individualized blood glucose level and formulate corresponding treatment principles to avoid hypoglycemia.

5.2 Intensive insulin therapy and inflammatory response

CABG under CPB is a clinically mature surgical method. With the continuous improvement of cardiovascular surgical technology and CPB, although the mortality of cardiac surgery has been greatly reduced, various stimulating factors often cause strong stress responses during CPB. It can not only produce stress hyperglycemia but also activate the complement system, resulting in the release of a large number of inflammatory factors, causing systemic inflammatory response syndrome (SIRS), accompanied by typical myocardial haemorrhage and reperfusion injury. SIRS is a self-amplifying and self-destructive inflammatory reaction. If its development is unbalanced, it can induce acute respiratory distress syndrome and multiple organ failure, which are important causes of mortality. A large number of clinical data show that intensive insulin therapy can not only effectively control blood glucose, but also significantly reduce the release of postoperative inflammatory factors, so as to reduce the incidence and mortality of clinical related complications, improve the prognosis of patients and accelerate the rehabilitation.

6. Objectives of glycemic control

Previous studies showed that the risk of infection in patients with postoperative blood glucose >12.2 mmol/l were 5 times higher than those with normal blood glucose. Once the postoperative blood glucose exceeds the normal level, it should be given hypoglycemic treatment, and it is more appropriate to control the blood glucose in the range of 4.0–6.1 mmol/l, which can effectively reduce a series of complications caused by hyperglycemia [21]. The increase of postoperative complications can affect or prolong the rehabilitation and hospital stay. Poor postoperative glycemic control will not only affect the healing but also increase the psychological and economic burden of patients. Insulin can be reasonably used to effectively control blood glucose before tracheal intubation is removed after operation. Patients who can eat after extubation can choose appropriate hypoglycemic drugs according to their condition to promote their rehabilitation. According to the results of Leuven Trail in 2001, intensive insulin control of blood glucose in ICU patients (< 6.1 mmol/l) can reduce the risk of death by 42% and the risk of related complications [22]. NICE-SUGAR study in 2009 is the largest multicenter study in ICU patients with intensive glycemic control [23]. The glycemic control goal of this study is < 6.1 mmol/l. The WSCTS guidelines suggested that both diabetics and non-diabetic patients should control their blood glucose below 10 mmol/L during cardiac surgery and early postoperative period, while the American Society of Clinical Endocrinology and the Endocrine Society (TES) recommended that the blood glucose of patients in the ICU should be maintained at 7.8–10.0 mmol/l.

7. Hypoglycemia

Currently, there is still no standard for the level of postoperative blood glucose, the amount of insulin and the treatment method. During insulin treatment, we
should closely observe the changes in blood glucose, adjust the amount of insulin and strictly control blood glucose. The main adverse reaction of insulin treatment is hypoglycemia. Hypoglycemia may be an important factor leading to the deterioration or death of critically severe patients, which should be closely monitored and actively treated. Because the symptoms and signs of hypoglycemia in anaesthetized or severe patients are not easy to be detected, strict blood glucose monitoring must be carried out in order to maintain the target blood glucose floating in a small range. A large number of studies have shown that hypoglycemia is a risk factor, and defined the methods to reduce its occurrence. Many studies have reported that ICU patients are more likely to have hypoglycemia when receiving intensive insulin therapy. Recent randomized controlled trials have also shown that hypoglycemia is a significant factor affecting the prognosis and may increase the risk of mortality intensive insulin therapy. Due to the potential safety hazards associated with hypoglycemia (including increased mortality) in intensive insulin therapy, some randomized trials were terminated. Hypoglycemia is the main risk of complications in long-term intensive control therapy. Clinically, it is necessary to personalize the treatment scheme of insulin hypoglycemic therapy and reset the target blood glucose value of intensive insulin therapy.

8. Significance of perioperative glycemic control

TES recently reported that the recommended treatment regimen is that the highest blood glucose concentration of ICU patients is maintained at 110 mg/dl, and the highest blood glucose level of other inpatients is maintained at 180 mg/dl. This view has been recognized by the National Association of Anesthesiologists. The American Heart Association recently published a specific recommendation for glycemic control. Based on the reported data and the advantages and disadvantages of glycemic control, it is suggested that the target glycemic control range of patients undergoing CABG operation is 120–150 mg/dl. This range will effectively reduce the complications and mortality of intraoperative and postoperative hyperglycemia, and reduce the risk of hypoglycemia. No matter what treatment plan is applied, patients should be closely monitored and diagnosed with hyperglycemia through laboratory analysis. In particular, hyperglycemia symptoms in anaesthetized patients may be covered up. These recommended treatments may change with the progress and improvements of science and technology. For example, continuous and reliable blood glucose measurement methods can be used clinically. Based on this, strict glycemic control and minimizing the related risks are possible.

Conflict of interest

The authors declare no conflict of interest.
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